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(54) Title: HUMAN TRANSCRIPTIONAL REGULATOR MOLECULES

(57) Abstract

The invention provides human transcriptional regulator molecules (HTRM) and polynucleotides which identify and encode HTRM. The invention also provides expression vectors, host cells, antibodies, agonists and antagonists. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of HTRM.

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HUMAN TRANSCRIPTIONAL REGULATOR MOLECULES

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of human transcriptional regulator molecules and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative and immune disorders.

BACKGROUND OF THE INVENTION

Differential control of gene expression is essential to the growth and development of all multicellular organisms. Although gene expression can be controlled at many steps along the path from DNA to protein, the major control point for most genes is at the initiation of transcription. This critical step is regulated both positively and negatively by a combination of general and tissue specific transcription factors, the majority of which function to regulate transcription of one or more target genes.

Mutations in transcription factors (TFs) contribute to oncogenesis. This is probably due to the role of transcription factors on the expression of genes involved in cell proliferation. For example, mutations in transcription factors encoded by proto-oncogenes, such as Fos, Jun, Myc, Rel, and Spi-1, may be oncogenic due to increased stimulation of cell proliferation. Conversely, mutations in transcription factors encoded by tumor suppressor genes, such as p53, RB1, and WT1, may be oncogenic due to decreased inhibition of cell proliferation. (Latchman, D. (1995) Gene Regulation: A Eukaryotic Perspective, Chapman and Hall, London, UK, pp 242-255.)

Many transcription factors are modular proteins that contain separate domains for DNA binding and transcriptional regulation. The DNA binding domain interacts with specific DNA sequences (control elements) near to or within the promoter region of the gene. This interaction brings the regulatory domain of the TF into a position where it can interact with other proteins to stimulate or repress transcription. Many TFs require dimerization or multimerization to be fully functional. Five different types of transcription factors have been described based on five well characterized structural motifs. These five types are the helix-turn-helix, zinc finger, leucine zipper, and helix-loop-helix (HLH) proteins and the steroid-hormone receptors.

The helix-turn-helix motif consists of two α helices held at a fixed angle. The two helices are connected by a short chain of amino acids, which represents the "turn". The more carboxyl-terminal helix is called the recognition helix and fits into the major groove of the DNA double helix. The recognition helix, whose amino acid side chains differ from protein to protein, plays an

important role in recognizing the specific DNA sequence to which the protein binds. All of the helix-turn-helix proteins bind DNA as dimers in which the two copies of the recognition helix are separated by exactly one turn of the DNA helix. Homeodomain proteins are a special class of helix-turn-helix protein. The homeodomain is folded into three α helices which are packed tightly together by hydrophobic interactions. Helices two and three closely resemble the helix-turn-helix motif, with the third helix acting as the recognition helix. Proteins containing homeodomain motifs often function as developmental switches.

The zinc finger motif consists of an α helix and antiparallel ß sheet held together by a zinc atom. The zinc finger motif is usually repeated in a tandem array within a protein, such that the α helix of each zinc finger in the protein makes contact with the major groove of the DNA double helix. This repeated contact between the protein and the DNA produces a strong and specific DNA-protein interaction. The strength and specificity of the interaction can be regulated by the number of zinc finger motifs within the protein.

The leucine zipper motif consists of a single α helix which is involved in both protein dimerization and DNA binding. Two proteins containing leucine zippers can dimerize by interactions between hydrophobic amino acid residues, commonly leucines, that extend from one side of their respective α helices. In this way, the α helices of each protein monomer dimerize to form a short coiled-coil. Just beyond this coiled-coil, the two α helices separate to form a Y-shaped structure which contacts the major groove of the DNA. Leucine zipper proteins may form homodimers, in which the two protein monomers are identical, or heterodimers, in which the two protein monomers are different. The specificity of DNA binding depends on the dimer formed, since each protein monomer has distinct DNA-binding specificities.

The helix-loop-helix (HLH) motif consists of a short α helix connected by a loop to a second, longer α helix. The flexible loop allows the two helices to fold back and pack together. As with the leucine zipper, the HLH motif is involved in both protein dimerization and DNA binding. The dimers can be homodimers or heterodimers, thus increasing the repertoire of DNA-binding sites to which HLH proteins can bind.

The steroid-hormone receptors contain a motif composed of two perpendicular α helices. In the absence of ligand the steroid-hormone receptors assume a conformation which sequesters the α helices. Binding of ligand, commonly steroid hormones, thyroid hormones, retinoids, or vitamin D, to the receptor causes a conformational change which exposes the α helices. The first α helix contains about seventy residues and includes eight conserved cysteines. This helix fits into the major groove of the DNA double helix and enables DNA-receptor binding. The second α helix provides for protein dimerization. As with leucine zipper and HLH proteins, both homodimers and heterodimers may be formed by steroid-hormone receptors.

Hundreds of regulatory proteins from a wide variety of organisms have been identified. Most of these proteins have at least one of the common structural motifs described. However, several important regulatory proteins, including the p53 tumor suppressor, have a unique structure not shared with other known regulatory molecules. (Faisst, S. and S. Meyer (1992) Nucl. Acids Res. 20:3-26.) Moreover, other domains of the regulatory proteins often form crucial contacts with the DNA, thereby affecting binding specificity. Accessory proteins can also provide important interactions which may convert a particular regulatory protein from an activator to a repressor, from a repressor to an activator, or it may prevent DNA binding by the regulatory protein completely.

The discovery of new human transcriptional regulator molecules and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative and immune disorders.

SUMMARY OF THE INVENTION

The invention features substantially purified polypeptides, human transcriptional regulator molecules, referred to collectively as "HTRM". In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of
SEQ ID NO:1-65, and fragments thereof.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID
NO:1-65, and fragments thereof. The invention also provides an isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of
SEQ ID NO:1-65, and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 70% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of
SEQ ID NO:1-65, and fragments thereof.

Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-65, and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino

acid sequence selected from the group consisting of SEQ ID NO:1-65, and fragments thereof.

The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:66-130, and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 70% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:66-130, and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:66-130, and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-65, and fragments thereof. In another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing at least a fragment of a polynucleotide under conditions suitable for the expression of the polypeptide; and (b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-65, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected from the group consisting of SEQ ID NO:1-65, and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder of cell proliferation associated with decreased expression or activity of HTRM, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-65, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder of cell proliferation associated with increased expression or activity of HTRM, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-65, and fragments thereof.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows nucleotide and polypeptide sequence identification numbers (SEQ ID NO), clone identification numbers (clone ID), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding HTRM.

Table 2 shows features of each polypeptide sequence including potential motifs, homologous sequences, and methods and algorithms used for identification of HTRM.

Table 3 shows the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis, diseases, disorders, or conditions associated with these tissues, and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which Incyte cDNA clones encoding HTRM were isolated.

Table 5 shows the programs, their descriptions, references, and threshold parameters used to analyze HTRM.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and

methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"HTRM" refers to the amino acid sequences of substantially purified HTRM obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which, when bound to HTRM, increases or prolongs the duration of the effect of HTRM. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules which bind to and modulate the effect of HTRM.

An "allelic variant" is an alternative form of the gene encoding HTRM. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. Any given natural or recombinant gene may have none, one, or many allelic forms. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding HTRM include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polynucleotide the same as HTRM or a polypeptide with at least one functional characteristic of HTRM. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding HTRM, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding HTRM. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent HTRM. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of HTRM is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, positively charged amino acids may include lysine and arginine, and amino acids with uncharged polar head groups having similar hydrophilicity values may include leucine, isoleucine, and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and

phenylalanine and tyrosine.

The terms "amino acid" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. In this context, "fragments," "immunogenic fragments," or "antigenic fragments" refer to fragments of HTRM which are preferably at least 5 to about 15 amino acids in length, most preferably at least 14 amino acids, and which retain some biological activity or immunological activity of HTRM. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which, when bound to HTRM, decreases the amount or the duration of the effect of the biological or immunological activity of HTRM. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules which decrease the effect of HTRM.

The term "antibody" refers to intact molecules as well as to fragments thereof, such as Fab, $F(ab')_2$, and Fv fragments, which are capable of binding the epitopic determinant. Antibodies that bind HTRM polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that fragment of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (given regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form

duplexes and to block either transcription or translation. The designation "negative" can refer to the antisense strand, and the designation "positive" can refer to the sense strand.

The term "biologically active," refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic HTRM, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" or "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acids strands, and in the design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" or a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding HTRM or fragments of HTRM may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of more than one Incyte Clone using a computer program for fragment assembly, such as the GELVIEW Fragment Assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

The term "correlates with expression of a polynucleotide" indicates that the detection of the presence of nucleic acids, the same or related to a nucleic acid sequence encoding HTRM, by northern analysis is indicative of the presence of nucleic acids encoding HTRM in a sample, and thereby correlates with expression of the transcript from the polynucleotide encoding HTRM.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" or "% identity" refer to the percentage of sequence similarity found in a comparison of two or more amino acid or nucleic acid sequences. Percent identity can be determined electronically, e.g., by using the MEGALIGN program (DNASTAR, Madison WI) which creates alignments between two or more sequences according to methods selected by the user, e.g., the clustal method. (See, e.g., Higgins, D.G. and P.M. Sharp (1988) Gene 73:237-244.) The clustal algorithm groups sequences into clusters by examining the distances between all pairs. The clusters are aligned pairwise and then in groups. The percentage similarity between two amino acid sequences, e.g., sequence A and sequence B, is calculated by dividing the length of sequence A, minus the number of gap residues in sequence A, minus the number of gap residues in sequence B, into the sum of the residue matches between sequence A and sequence B, times one hundred. Gaps of low or of no similarity between the two amino acid

sequences are not included in determining percentage similarity. Percent identity between nucleic acid sequences can also be counted or calculated by other methods known in the art, e.g., the Jotun Hein method. (See, e.g., Hein, J. (1990) Methods Enzymol. 183:626-645.) Identity between sequences can also be determined by other methods known in the art, e.g., by varying hybridization conditions.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" or "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively, to the sequence found in the naturally occurring molecule.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" or "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

The term "modulate" refers to a change in the activity of HTRM. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of HTRM.

The phrases "nucleic acid" or "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may

represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material. In this context, "fragments" refers to those nucleic acid sequences which, when translated, would produce polypeptides retaining some functional characteristic, e.g., antigenicity, or structural domain characteristic, e.g., ATP-binding site, of the full-length polypeptide.

The terms "operably associated" or "operably linked" refer to functionally related nucleic acid sequences. A promoter is operably associated or operably linked with a coding sequence if the promoter controls the translation of the encoded polypeptide. While operably associated or operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements, e.g., repressor genes, are not contiguously linked to the sequence encoding the polypeptide but still bind to operator sequences that control expression of the polypeptide.

The term "oligonucleotide" refers to a nucleic acid sequence of at least about 6 nucleotides to 60 nucleotides, preferably about 15 to 30 nucleotides, and most preferably about 20 to 25 nucleotides, which can be used in PCR amplification or in a hybridization assay or microarray. "Oligonucleotide" is substantially equivalent to the terms "amplimer," "primer," "oligomer," and "probe," as these terms are commonly defined in the art.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding HTRM, or fragments thereof, or HTRM itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" or "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, or an antagonist. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other

conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

"Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "variant" of HTRM polypeptides refers to an amino acid sequence that is altered by one or more amino acid residues. The variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties (e.g., replacement of leucine with isoleucine). More rarely, a variant may have "nonconservative" changes (e.g., replacement of glycine with tryptophan). Analogous minor variations may also include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing biological or immunological activity may be found using computer programs well known in the art, for example, LASERGENE software (DNASTAR).

The term "variant," when used in the context of a polynucleotide sequence, may encompass a polynucleotide sequence related to HTRM. This definition may also include, for example, "allelic" (as defined above), "splice," "species," or "polymorphic" variants. A splice variant may have significant identity to a reference molecule, but will generally have a greater or

lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or an absence of domains. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

THE INVENTION

The invention is based on the discovery of new human transcriptional regulator molecules (HTRM), the polynucleotides encoding HTRM, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative and immune disorders.

Table 1 lists the Incyte Clones used to derive full length nucleotide sequences encoding HTRM. Columns 1 and 2 show the sequence identification numbers (SEQ ID NO) of the amino acid and nucleic acid sequences, respectively. Column 3 shows the Clone ID of the Incyte Clone in which nucleic acids encoding each HTRM were identified, and column 4, the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones, their corresponding cDNA libraries, and shotgun sequences. The clones and shotgun sequences are part of the consensus nucleotide sequence of each HTRM and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3, potential phosphorylation sites; column 4, potential glycosylation sites; column 5, the amino acid residues comprising signature sequences and motifs; column 6, the identity of each protein; and column 7, analytical methods used to identify each protein through sequence homology and protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding HTRM. The first column of Table 3 lists the nucleotide sequence identifiers. The second column lists tissue categories which express HTRM as a fraction of total tissue categories expressing HTRM. The third column lists the diseases, disorders, or conditions associated with those tissues expressing HTRM. The fourth column lists the vectors used to subclone the cDNA library.

The following fragments of the nucleotide sequences encoding HTRM are useful in hybridization or amplification technologies to identify SEQ ID NO:110-130 and to distinguish between SEQ ID NO:110-130 and related polynucleotide sequences. The useful fragments are the

fragment of SEQ ID NO:110 from about nucleotide 273 to about nucleotide 317: the fragment of SEQ ID NO:111 from about nucleotide 217 to about nucleotide 261 the fragment of SEQ ID NO:112 from about nucleotide 273 to about nucleotide 308; the fragment of SEQ ID NO:113 from about nucleotide 163 to about nucleotide 207; the fragment of SEQ ID NO: 114 from about nucleotide 433 to about nucleotide 477; the fragment of SEQ ID NO:115 from about nucleotide 597 to about nucleotide 641; the fragment of SEQ ID NO:116 from about nucleotide 111 to about nucleotide 146; the fragment of SEQ ID NO:117 from about nucleotide 217 to about nucleotide 261; the fragment of SEQ ID NO:118 from about nucleotide 867 to about nucleotide 911; the fragment of SEQ ID NO:119 from about nucleotide 1082 to about nucleotide 1126; the fragment of SEQ ID NO:120 from about nucleotide 702 to about nucleotide 748; the fragment of SEQ ID NO:121 from about nucleotide 380 to about nucleotide 424; the fragment of SEQ ID NO:122 from about nucleotide 352 to about nucleotide 396; the fragment of SEQ ID NO: 123 from about nucleotide 219 to about nucleotide 263; the fragment of SEQ ID NO:124 from about nucleotide 326 to about nucleotide 370; the fragment of SEQ ID NO:125 from about nucleotide 595 to about nucleotide 639; the fragment of SEQ ID NO:126 from about nucleotide 272 to about nucleotide 316; the fragment of SEQ ID NO:127 from about nucleotide 163 to about nucleotide 207; the fragment of SEQ ID NO:128 from about nucleotide 271 to about nucleotide 315; the fragment of SEQ ID NO:129 from about nucleotide 866 to about nucleotide 910; and the fragment of SEQ ID NO:130 from about nucleotide 487 to about nucleotide 531.

The invention also encompasses HTRM variants. A preferred HTRM variant is one which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the HTRM amino acid sequence, and which contains at least one functional or structural characteristic of HTRM.

The invention also encompasses polynucleotides which encode HTRM. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:66-130, which encodes HTRM.

The invention also encompasses a variant of a polynucleotide sequence encoding HTRM. In particular, such a variant polynucleotide sequence will have at least about 70%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding HTRM. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID
NO:66-130 which has at least about 70%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:66-130. Any one of the polynucleotide variants described above

can encode an amino acid sequence which contains at least one functional or structural characteristic of HTRM.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding HTRM, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring HTRM, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode HTRM and its variants are preferably capable of hybridizing to the nucleotide sequence of the naturally occurring HTRM under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding HTRM or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding HTRM and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode HTRM and HTRM derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding HTRM or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:66-130 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide.

and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the Hamilton MICROLAB 2200 (Hamilton, Reno NV), Peltier Thermal Cycler 200 (PTC200; MJ Research, Watertown MA) and the ABI CATALYST 800 (Perkin-Elmer). Sequencing is then carried out using either ABI 373 or 377 DNA sequencing systems (Perkin-Elmer) or the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA). The resulting sequences are analyzed using a variety of

algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding HTRM may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-306). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer),

and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode HTRM may be cloned in recombinant DNA molecules that direct expression of HTRM, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express HTRM.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter HTRM-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding HTRM may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucl. Acids Res. Symp. Ser. 215-223, and Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 225-232.) Alternatively, HTRM itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of HTRM, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g, Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

In order to express a biologically active HTRM, the nucleotide sequences encoding HTRM or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as

enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding HTRM. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding HTRM. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding HTRM and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding HTRM and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding HTRM. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding HTRM. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding HTRM can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or pSPORT1 plasmid (Life Technologies). Ligation of sequences encoding HTRM into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these

vectors may be useful for in vitro transcription. dideoxy sequencing. single strand rescue with helper phage. and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of HTRM are needed. e.g. for the production of antibodies. vectors which direct high level expression of HTRM may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of HTRM. A number of vectors containing constitutive or inducible promoters, such as alpha factor. alcohol oxidase, and PGH, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Grant et al. (1987) Methods Enzymol. 153:516-54; and Scorer, C. A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of HTRM. Transcription of sequences encoding HTRM may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding HTRM may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses HTRM in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of HTRM in cell lines is preferred. For example, sequences encoding HTRM can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk⁻* or *apr⁻* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides, neomycin and G-418; and *als* or *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate ß-glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding HTRM is inserted within a marker gene sequence, transformed cells containing sequences encoding HTRM can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding HTRM under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding HTRM and that express HTRM may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR

amplification. and protein bioassay or immunoassay techniques which include membrane. solution. or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of HTRM using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on HTRM is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St Paul MN. Sect. IV; Coligan, J. E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding HTRM include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding HTRM, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding HTRM may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode HTRM may be designed to contain signal sequences which direct secretion of HTRM through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation,

phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38), are available from the American Type Culture Collection (ATCC, Bethesda MD) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding HTRM may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric HTRM protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of HTRM activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the HTRM encoding sequence and the heterologous protein sequence, so that HTRM may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled HTRM may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract systems (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, preferably ^{35}S-methionine.

Fragments of HTRM may be produced not only by recombinant production, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Various fragments of HTRM may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of HTRM and human transcriptional regulator molecules. In addition, the expression of HTRM is closely associated with cell proliferation, inflammation, and the immune response. Therefore, HTRM appears to play a role in cell proliferative and immune disorders. In the treatment of disorders associated with increased HTRM expression or activity, it is desirable to decrease the expression or activity of HTRM. In the treatment of disorders associated with decreased HTRM expression or activity, it is desirable to increase the expression or activity of HTRM.

Therefore, in one embodiment, HTRM or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HTRM. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia; cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; and an immune disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma

In another embodiment, a vector capable of expressing HTRM or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HTRM including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified HTRM in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HTRM including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of HTRM may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HTRM including, but not limited to, those listed above.

In a further embodiment, an antagonist of HTRM may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of HTRM. Examples of such disorders include, but are not limited to, those described above. In one aspect, an antibody which specifically binds HTRM may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissue which express HTRM.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding HTRM may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of HTRM including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of HTRM may be produced using methods which are generally known in the art. In particular, purified HTRM may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind HTRM. Antibodies to HTRM may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are especially preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with HTRM or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not

limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to HTRM have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of HTRM amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to HTRM may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce HTRM-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton D.R. (1991) Proc. Natl. Acad. Sci. 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for HTRM may also be generated. For example, such fragments include, but are not limited to, F(ab')2 fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired

specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between HTRM and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering HTRM epitopes is preferred, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for HTRM. Affinity is expressed as an association constant, K_a, which is defined as the molar concentration of HTRM-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple HTRM epitopes, represents the average affinity, or avidity, of the antibodies for HTRM. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular HTRM epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the HTRM-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of HTRM, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J. E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is preferred for use in procedures requiring precipitation of HTRM-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding HTRM, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding HTRM may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding HTRM. Thus, complementary molecules

or fragments may be used to modulate HTRM activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding HTRM.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding HTRM. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding HTRM can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding HTRM. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding HTRM. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, are preferred. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding HTRM.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20

ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding HTRM. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nature Biotechnology 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of HTRM, antibodies to HTRM, and mimetics, agonists, antagonists, or inhibitors of HTRM. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical

carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty

oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of HTRM, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example HTRM or fragments thereof, antibodies of HTRM, and agonists, antagonists or inhibitors of HTRM, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind HTRM may be used for the diagnosis of disorders characterized by expression of HTRM, or in assays to monitor patients being treated with HTRM or agonists, antagonists, or inhibitors of HTRM. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for HTRM include methods which utilize the antibody and a label to detect HTRM in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known

in the art and may be used.

A variety of protocols for measuring HTRM, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of HTRM expression. Normal or standard values for HTRM expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to HTRM under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of HTRM expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding HTRM may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of HTRM may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of HTRM, and to monitor regulation of HTRM levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding HTRM or closely related molecules may be used to identify nucleic acid sequences which encode HTRM. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding HTRM, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the HTRM encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:66-130 or from genomic sequences including promoters, enhancers, and introns of the HTRM gene.

Means for producing specific hybridization probes for DNAs encoding HTRM include the cloning of polynucleotide sequences encoding HTRM or HTRM derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes <u>in vitro</u> by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S, or by enzymatic labels.

such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding HTRM may be used for the diagnosis of disorders associated with expression of HTRM. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia; cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; and an immune disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma. The polynucleotide sequences encoding HTRM may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered HTRM expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding HTRM may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding HTRM may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantitated and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding HTRM in the sample indicates the presence of the associated disorder. Such

assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of HTRM, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding HTRM, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding HTRM may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding HTRM, or a fragment of a polynucleotide complementary to the polynucleotide encoding HTRM, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantitation of closely related DNA or RNA sequences.

Methods which may also be used to quantitate the expression of HTRM include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in an ELISA format where the oligomer of interest is presented in various dilutions and a spectrophotometric or

colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding HTRM may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) site. Correlation between the location of the gene encoding HTRM on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been

crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, HTRM, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between HTRM and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with HTRM, or fragments thereof, and washed. Bound HTRM is then detected by methods well known in the art. Purified HTRM can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding HTRM specifically compete with a test compound for binding HTRM. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with HTRM.

In additional embodiments, the nucleotide sequences which encode HTRM may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any was whatsoever.

The entire disclosure of all applications, patents, and publications, cited above and below, and of US provisional applications 60/084,254 (filed May 5, 1998), 60/095,827 (filed August 7, 1998), and 60/102,745 (filed Oct. 2, 1998) are hereby incorporated by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Valencia CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6). Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), pSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5α, DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by in vivo excision, using the UNIZAP vector system (Stratagene) or cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the REAL Prep 96 plasmid kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a Fluoroskan II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

The cDNAs were prepared for sequencing using the ABI CATALYST 800 (Perkin-Elmer) or the HYDRA microdispenser (Robbins Scientific) or MICROLAB 2200 (Hamilton) systems in combination with the PTC-200 thermal cyclers (MJ Research). The cDNAs were sequenced using the ABI PRISM 373 or 377 sequencing systems (Perkin-Elmer) and standard ABI protocols, base calling software, and kits. In one alternative, cDNAs were sequenced using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics). In another alternative, the cDNAs were amplified and sequenced using the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). In yet another alternative, cDNAs were sequenced using solutions and dyes from Amersham Pharmacia Biotech. Reading frames for the ESTs were determined using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA, extension, and shotgun sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the software programs, descriptions, references, and threshold parameters used. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides a brief description thereof, the third column presents the references which are incorporated by reference herein, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the probability the greater the homology). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, S. San Francisco CA) and LASERGENE software (DNASTAR).

cDNAs were also compared to sequences in GenBank using a search algorithm developed by Applied Biosystems and incorporated into the INHERIT™ 670 sequence analysis system. In this algorithm, Pattern Specification Language (TRW Inc, Los Angeles, CA) was used to determine regions of homology. The three parameters that determine how the sequence comparisons run were window size, window offset, and error tolerance. Using a combination of these three parameters, the DNA database was searched for sequences containing regions of homology to the query sequence, and the appropriate sequences were scored with an initial value.

Subsequently, these homologous regions were examined using dot matrix homology plots to distinguish regions of homology from chance matches. Smith-Waterman alignments were used to display the results of the homology search.

Peptide and protein sequence homologies were ascertained using the INHERIT- 670 sequence analysis system using the methods similar to those used in DNA sequence homologies. Pattern Specification Language and parameter windows were used to search protein databases for sequences containing regions of homology which were scored with an initial value. Dot-matrix homology plots were examined to distinguish regions of significant homology from chance matches.

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS to acquire annotation, using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, PFAM, and Prosite.

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:110-130 Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ database (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score,

which is defined as:

$$\frac{\%\ \text{sequence identity} \times \%\ \text{maximum BLAST score}}{100}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported a percentage distribution of libraries in which the transcript encoding HTRM occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease categories included cancer, inflammation/trauma, fetal, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease expression are reported in Table 3.

V. Extension of HTRM Encoding Polynucleotides

The full length nucleic acid sequence of SEQ ID NO:66-130 was produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+}, $(NH_4)_2SO_4$, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min: Step 2: 94°C, 15 sec: Step 3: 60°C, 1 min; Step 4: 68°C, 2 min: Step 5: Steps 2, 3, and 4 repeated 20 times: Step 6: 68°C, 5 min: Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+

were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 μl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μl to 10 μl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulphoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequence of SEQ ID NO:66-130 is used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:66-130 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20

base pairs. is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer. 250 μCi of [γ-^{32}P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba1, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under increasingly stringent conditions up to 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. After XOMAT-AR film (Eastman Kodak, Rochester NY) is exposed to the blots to film for several hours, hybridization patterns are compared visually.

VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, supra.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

VIII. Complementary Polynucleotides

Sequences complementary to the HTRM-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring HTRM. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of HTRM. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the HTRM-encoding transcript.

IX. Expression of HTRM

Expression and purification of HTRM is achieved using bacterial or virus-based expression systems. For expression of HTRM in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express HTRM upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of HTRM in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding HTRM by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E. K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, HTRM is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from HTRM at specifically engineered sites. FLAG, an 8-amino acid

peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch 10 and 16). Purified HTRM obtained by these methods can be used directly in the following activity assay.

X. Demonstration of HTRM Activity

HTRM activity is measured by its ability to stimulate transcription of a reporter gene, essentially as described in Liu, H.Y., et al (1997; EMBO J. 16:5289-5298.). The assay entails the use of a well characterized reporter gene construct, $LexA_{op}$-LacZ, that consists of LexA DNA transcriptional control elements ($LexA_{op}$) fused to sequences encoding the E. coli β-galactosidase enzyme (LacZ). The methods for fusion gene contruction, expression, and introduction into cells, and measurement of β-galactosidase enzyme activity, are well known to those skilled in the art. Sequences encoding HTRM are cloned into a plasmid that directs the synthesis of a fusion protein, LexA-HTRM, consisting of HTRM and a DNA binding domain derived from the LexA transcription factor. The plasmid encoding the LexA-HTRM fusion protein is introduced into yeast cells along with the plasmid containing the $LexA_{op}$-LacZ reporter gene. The amount of β-galactosidase enzyme activity associated with LexA-HTRM transfected cells, relative to control cells, is proportional to the amount of transcription stimulated by the HTRM gene product.

XI. Functional Assays

HTRM function is assessed by expressing the sequences encoding HTRM at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, preferably of endothelial or hematopoietic origin, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP, and to evaluate properties, for example, their apoptotic state. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA

content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M. G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of HTRM on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding HTRM and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding HTRM and other genes of interest can be analyzed by northern analysis or microarray techniques.

XII. Production of HTRM Specific Antibodies

HTRM substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the HTRM amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides 15 residues in length are synthesized using an ABI 431A Peptide Synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide activity by, for example, binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIII. Purification of Naturally Occurring HTRM Using Specific Antibodies

Naturally occurring or recombinant HTRM is substantially purified by immunoaffinity chromatography using antibodies specific for HTRM. An immunoaffinity column is constructed by covalently coupling anti-HTRM antibody to an activated chromatographic resin, such as

CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing HTRM are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of HTRM (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/HTRM binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and HTRM is collected.

XIV. Identification of Molecules Which Interact with HTRM

HTRM, or biologically active fragments thereof, are labeled with ^{125}I Bolton-Hunter reagent. (See, e.g., Bolton et al. (1973) Biochem. J. 133:529.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled HTRM, washed, and any wells with labeled HTRM complex are assayed. Data obtained using different concentrations of HTRM are used to calculate values for the number, affinity, and association of HTRM with the candidate molecules.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	66	001106	U937NOT01	001106 (U937NOT01), 1291142 (BRAINOT11), 2590425 (LUNGNOT22), 1300570 (BRSTNOT07)
2	67	004586	HMC1NOT01	004586 (HMC1NOT01), 3889843 (BRSTTUT16), 1432988 (BEPINON01), 788995 (PROSTUT03), 1605475 (LUNGNOT15)
3	68	052927	FIBRNOT01	052927 (FIBRNOT01), 2518848 (BRAITUT21), 3520218 (LUNGNON03), 086878 (LIVRNOT01)
4	69	082843	HUVESTB01	082843 (HUVESTB01), 4008105 (ENDCNOT04), 2083528(UTRSNOT08), 2345764 (TESTTUT02), 3771780 (BRSTNOT25), 190782 (CONNTUT01), 2206259 (SPLNFET02), 2509193 (CONUTUT01)
5	70	322349	EOSIHET02	322349 (EOSIHET02), 3686018 (HEAANOT01), 1853592(LUNGFET03), 815966 (OVARTUT01), 1505002 (BRAITUT07), 1511883 (LUNGNOT14), 2232826 (PROSNOT16)
6	71	397663	PITUNOT02	397663 (PITUNOT02), 491141 (HNT2AGT01), 3809879(CONTTUT01) 3562349 (SKINNOT05), 1518413 (BLADTUT04), 3600151 (DRGTNOT01), 2474103 (THP1NOT03), 2105304 (BRAITUT03),2187330 (PROSNOT26), 1781572 (PGANNON02), 2056258 (BEPINOT01), 1888065 (BLADTUT07)
7	72	673766	CRBLNOT01	673766 (CRBLNOT01), 2494421 (ADRETUT05), 3267748 (BRAINOT20) 2194042 (THYRTUT03), 3186455 (THYMNON04), 1712236 (PROSNOT16) 1844092 (COLNNOT08), 1602283 (BLADNOT03), 033357 (THP1NOB01), 1995828 (BRSTTUT03), 1485594 (CORPNOT02)
8	73	1504753	BRAITUT07	1504753 (BRAITUT07), 633939 (NEUTGMT01), 2741379 (BRSTTUT14), 2959661 (ADRENOT09), 3483904 (KIDNNOT31), 999401 (KIDNTUT01), 1965504 (BRSTNOT04), 588535 (UTRSNOT01)
9	74	1760185	PITUNOT03	1760085 (PITUNOT03), 1914471 (PROSTUT04), 836831(PROSNOT07), 729798 (LUNGNOT03), 1290847 (BRAINOT11), 1492387 (PROSNON01),1368472 (SCORNON02)

Table 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
10	75	1805061	SINTNOT13	1805061 (SINTNOT13), 1435949 (PANCNOT08), 086122(LIVRNOT01) 1482366 (CORPNOT02), 1835310 (BRAINON01), 1333758 (COLNNOT13), 3521449 (LUNGNON03)
11	76	1850120	LUNGFET03	1850120 (LUNGFET03), 3126350 (LUNGTUT12), 786916 (PROSNOT05) 2899740 (DRGCNOT01), 1259221 (MENITUT03), 1334740 (COLNNOT13), 2466350 (THYRNOT08)
12	77	1852290	LUNGFET03	1852290 (LUNGFET03), 2901081 (DRGCNOT01), 1384842(BRAITUT08) 1293541 (PGANNOT03), 1964126 (BRSTNOT04)
13	78	1944530	PITUNOT01	1944530 (PITUNOT01), 2808142 and 2809196 (BLADTUT08), 2961779 (ADRENOT09)
14	79	2019742	CONNNOT01	2019742 (CONNNOT01), 2968014 (SCORNOT04), 168472 (LIVRNOT01) 1875993 (LEUKNOT02), 1522480 (BLADTUT04), 1418496 (KIDNNOT09), 149730 (FIBRNGT02)
15	80	2056042	BEPINOT01	2056042 (BEPINOT01), 3097391 (CERVNOT03), 1985203 (LUNGAST01) 1962619 (BRSTNOT04), 1335716(COLNNOT13)
16	81	2398682	THP1AZT01	2398682 (THP1AZT01), 159706 (ADENINB01), 2443910(THP1NOT03) 2382189 (ISLTNOT01), 2288661 (BRAINON01), 1864422(PROSNOT19)
17	82	2518753	BRAITUT21	2518753 (BRAITUT21), 4001219 (HNT2AZS07), 2606361 (LUNGTUT07) 449043 (TLYMNOT02), SAEA01390
18	83	2709055	PONSAZT01	2709055 (PONSAZT01), 2309703 (NGANNOT01), 1661042 (URETTUT01), 2761284 (ESOGTUT02), 2469634 (THP1NOT03), SBLA03183, SBLA00549 SBLA00975
19	84	2724537	LUNGTUT10	2724537 (LUNGTUT10), 3869823 (BMARNOT03), 952779 (SCORNON01), 2049127 (LIVRFET02), 1824284 (GBLATUT01), 1870588 and 1869666 (SKINBIT01), 2626505 (PROSTUT12), SAEA03404, SAEA01744 SAEA01672, SAEA10045, SAPA04072, SAPA00149

Table 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragment
20	85	025818	SPLNFET01	025818H1, 025818X12, and 025818X3 (SPLNFET01), 783259H1 (MYOMNOT01), 826162R1 (PROSNOT06)
21	86	438283	THYRNOT01	438283H1 and 438283X29 (THYRNOT01), SAGA01136F1, SAGA01671F1, SAGA02704F1, SAGA03722F1, SZZZ01038R1
22	87	619699	PGANNOT01	619699H1, 619699X11, and 619699X18 (PGANNOT01), 646198T6 (BRSTTUT02), 1322305X20F1 (BLADNOT04), 1724376F6 (PROSNOT14)
23	88	693452	SYNORAT03	118140R1 (MUSCNOT01), 693452H1 and 693452R6 (SYNORAT03), 2455538F6 and 2455538H1 (ENDANOT01), 4500333H1 (BRAVTXT02)
24	89	839651	PROSTUT05	729341X12 (LUNGNOT03), 839651CT1, 839651H1, and 839651X55 (PROSTUT05), 839651X60 (PROSTUT05)
25	90	1253545	LUNGFET03	1253545H1 and 1254914F6 (LUNGFET03), 1806337X13F1 and 1807402X11F1 (SINTNOT13), 2179882X22F1 (SININOT01), 2592938F6 (LUNGNOT22), 2840018F6 (DRGLNOT01)
26	91	1425691	BEPINON01	2727135H1 (OVARTUT05), 587126X29R1, 588598X17, and 587126F1 (UTRSNOT01), 1714529F6 (UCMCNOT02), 1381341F6 (BRAITUT08), 1273513F6 (TESTTUT02), 060265R1(LUNGNOT01), 1459659F1 (COLNFET02), 043139R1 (TBLYNOT01), 1425691H1 (BEPINON01

Table 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
27	92	1484257	CORPNOT02	400685H1, 404702F1, 404702R6, 404702X45C1, 404702X47C1, and 404702X48C1 (TMLR3DT01), 1484257H1 (CORPNOT02), 3396312H1 (UTRSNOT16)
28	93	1732368	BRSTTUT08	920006H1 (RATRNOT02), 1732368F6 and 1732368H1 (BRSTTUT08), 2607269T6 (LUNGTUT07), 2654363F6 (THYMNOT04)
29	94	1870914	SKINBIT01	1549551R6 (PROSNOT06), 1575349H1 (LNODNOT03), 1870914H1 (SKINBIT01), 2365851T6 (ADRENOT07), SBKA00149F1
30	95	1910984	CONNTUT01	859876X12 (BRAITUT03), 1234976H1 and 1241845H1 (LUNGNOT03), 1910984F6 and 1910984H1 (CONNTUT01), 3276505H1 (PROSBPT06)
31	96	1943040	HIPONOT01	824144R1 (PROSNOT06), 930281H1 (CERVNOT01), 1420545H1 (KIDNNOT09), 1784405H1 (BRAINOT10), 1943040H1 and 1943040R6 (HIPONOT01), 2122271H1 (BRSTNOT07), 2729723H1 (OVARTUT04)
32	97	2076520	ISLTNOT01	419755R1 (BRSTNOT01), 954937R1 (KIDNNOT05), 1460268H1 (COLNFET02), 1599016H1 (BLADNOT03), 2076520H1 (ISLTNOT01), 2082255F6 (UTRSNOT08), 2184150F6 (SININOT01), 2884394F6 (SINJNOT02), 3726575H1 (BRSTNOT23), 3752466H1 (UTRSNOT18), 3764971H1 (BRSTNOT24), 4412005H1 (MONOTXT01

Table 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
33	98	2291241	BRAINON01	2291241CT1 and 2291241H1 (BRAINON01), 2500586H1 (ADRETUT05)
34	99	2329692	COLNNOT11	158014F1 (ADENINB01), 1519462F1 (BLADTUT04), 1543875R1 (PROSTUT04), 2329692H1, 2331530R6, and 2331530T6 (COLNNOT11), 2478291F6 (SMCANOT01)
35	100	2474110	THP1NOT03	863265H1 (BRAITUT03), 1313444F1 (BLADTUT02), 1872631T6 and 1872869F6 (LEUKNOT02), 2061219R6 (OVARNOT03), 2171863H1 (ENDCNOT03), 2474110H1 (THP1NOT03), 2690250H1 (LUNGNOT23), 2812791F6 (OVARNOT10)
36	101	2495790	ADRETUT05	1360349T1 (LUNGNOT12), 1689792H1 (PROSTUT10), 1795321H1 (PROSTUT05), 1905521F6 (OVARNOT07), 1907168F6 (OVARNOT07), 2495790H1 (ADRETUT05), 2587542F6 (BRAITUT22)
37	102	2661254	ADRENOT08	1241850H1 (LUNGNOT03), 1545867R1 (PROSTUT04), 2325561H1 (OVARNOT02), 2661254H1 (ADRENOT08), 2751457H1 (THP1AZS08)
38	103	2674047	KIDNNOT19	489330H1 (HNT2AGT01), 2059316R6 (OVARNOT03), 2059316T6 (OVARNOT03), 2674047F6 and 2674047H1 (KIDNNOT19), 2805474H1 (BLADTUT08), 3076605H1 (BONEUNT01), 3080137T6 (BRAIUNT01)

Table 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
39	104	2762174	BRAINOS12	2573448T3 (HIPOAZT01), 2762174H1 (BRAINOS12), SBNA00508F1, SBNA01683F1, SBNA00674F1, SBNA00857F1
40	105	2765991	BRSTNOT12	082008R6 (HUVESTB01), 2127491T6 (KIDNNOT05), 2765991F6 and 2765991H1 (BRSTNOT12), 3147681H1 (PENCNOT05), SZAH01537F1, SZAH01356F1
41	106	2775157	PANCNOT15	2325410H1 (OVARNOT02), 2506671F6 and 2506671T6 (CONUTUT01), 2775157F6 and 2775157H1 (PANCNOT15), 3376091F6 (PENGNOT01), 3412063H1 (BRSTTUS08)
42	107	2918375	THYMFET03	227782F1 (PANCNOT01), 1225559H1 (COLNTUT02), 1511458T1 (LUNGNOT14), 2918375H1 (THYMFET03)
43	108	3149729	ADRENON04	605315F1 (BRSTTUT01), 3149729CT1 and 3149729H1 (ADRENON04)
44	109	3705895	PENCNOT07	744201R1 (BRAITUT01), 2550322H1 (LUNGTUT06), 3705895H1 (PENCNOT07)

Table 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
45	110	003256	HMC1NOT01	003256H1, 003256R6, 003256T6, 003256X305F1, 003256X313F, 003256X315F1, and 009404H1 (HMC1NOT01), 43104R1 (TBLYNOT01), 413017F1 (BRSTNOT01)
46	111	156986	THP1PLB02	010084F1 and 012909H1 (THP1PLB01), 156986H1 and 156986R1 (THP1PLB02), 1320255F1 (BLADNOT04), 1512255F1 (LUNGNOT14), 2061923T6 (OVARNOT03), 2398787F6 (THP1AZT01), 2517160H2 (LIVRTUT04)
47	112	319415	EOSIHET02	285773H1, 285773R1, 319415H1, and 319415X19F1 (EOSIHET02), 1231455H1 (BRAITUT01), 1804042F6 (SINTNOT13), 1878858F6 (LEUKNOT03)
48	113	635581	NEUTGMT01	635581H1 (NEUTGMT01), 3045776F6 (HEAANOT01)
49	114	921803	RATRNOT02	921803H1 (RATRNOT02), 1275128T6 (TESTTUT02), 1709959F6 (PROSNOT16), 2416547F6 (HNT3AZT01), 3016146H1 (MUSCNOT07), 3577260H1 (BRONNOT01)
50	115	1250492	LUNGFET03	691921X14F1 (LUNGTUT02), 1250492F6, 1250492H1, and 1252265F2 (LUNGFET03), 1361644F6 (LUNGNOT12), 3049358F6 (LUNGNOT25), 4044523H1 and 4048275H1 (LUNGNOT35), 4145295H1 (SINITUT04)
51	116	1427838	SINTBST01	1261181H1 (SYNORAT05), 1427838H1 and 1427838T1 (SINTBST01), 1733769T6 (BRSTTUT08), 2551854H1 (LUNGTUT06)
52	117	1448258	PLACNOT02	1448258H1 and 1448258R1 (PLACNOT02), 1484126F1 (CORPNOT02), 1856631F6 and 1856631X11F1 (PROSNOT18), 2690070F6 (LUNGNOT23), SAMA00131F1 and SAMA00146F1

Table 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
53	118	1645941	PROSTUT09	831680R6 (PROSTUT04), 1645941F6 and 1645941H1 (PROSTUT09), 1748682F6 (STOMTUT02), 1870831F6 (SKINBIT01), 1877907F6 (LEUKNOT03), 2310427R6 (NGANNOT01)
54	119	1646005	PROSTUT09	1646005H1, 1646005X309F1, 1646005X312F1 and 1646883F6 (PROSTUT09), SZAH02276F1
55	120	1686561	PROSNOT15	1234124H1 (LUNGFET03), 1299156F6 (BRSTNOT07), 1425185R1 (BEPINON01), 1544751T1 (PROSTUT04), 1686561H1 (PROSNOT15), 2723108H1 (LUNGTUT10), 2752156H1 (THP1AZS08), 3335850F6 (BRAIFET01), 3502259H1 (ADRENOT11), 3857461H1 (LNODNOT03), 5069547H1 (PANCNOT23)
56	121	1821233	GBLATUT01	030744H1 (THP1NOB01), 1272043F1 (TESTTUT02), 1419549F1 (KIDNNOT09), 1433773R1 (BEPINON01), 1482848F1 (CORPNOT02), 1821233H1 (GBLATUT01), 1869022H1 (SKINBIT01)
57	122	1877278	LEUKNOT03	1871148F6 (SKINBIT01), 1877278H1 (LEUKNOT03), 2097362T6 (BRAITUT02), 3124246T6 (LNODNOT05), 3450007R6 (UTRSNON03), 4894340H1 (LIVRTUT12), SAEB02108R1
58	123	1880692	LEUKNOT03	1880692H1 (LEUKNOT03), SBAA00446F1, SARA03727F1

Table 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
59	124	2280456	PROSNON01	1557906F6 (BLADTUT04), 2280456H1 (PROSNON01), 2799446F6 (NPOLNOT01), 3519009H1 (LUNGNON03)
60	125	2284580	BRAINON01	783560H1 (MYOMNOT01), 1215190T2 (BRSTTUT01), 1458188F1 (COLNFET02), 2284580H1 (BRAINON01), 2398366F6 (THP1AZT01), 2469268H1 (THP1NOT03)
61	126	2779172	OVARTUT03	487548H1 and 487548R6 (HNT2AGT01), 1421684F1 (KIDNNOT09), 2172754F6 (ENDCNOT03), 2672062F6 (ESOGTUT02), 2779172F6 and 2779172H1 (OVARTUT03), 2935502F6 (THYMFET02), 3206879F6 (PENCNOT03)
62	127	3279329	STOMFET02	885282R6 and 885282T1 (PANCNOT05), 901139R1 (BRSTTUT03), 1655530F6 (PROSTUT08), 1818669T6 (PROSNOT20), 2380664F6 (ISLTNOT01), 2921229H1 (SININOT04), 3279329H1 (STOMFET02), 3451425R6 (UTRSNON03)
63	128	3340290	SPLNNOT10	102935H1 (ADRENOR01), 1363193F6 (LUNGNOT12), 1674514H1 (BLADNOT05), 2271374H1 (PROSNON01), 2827770H1 (TLYMNOT03), 3340290H1 (SPLNNOT10), 4556330H1 (KERAUNT01)
64	129	3376404	PENGNOT01	3376404H1, 3376404X300U1, 3376404X310U1, and 3376404X323U1 (PENGNOT01), 3741323X302B1 (MENTNOT01)
65	130	4173111	SINTNOT21	1337315F6 (COLNNOT13), 2486184F6 (CONUTUT01), 4173111H1 (SINTNOT21), 4750042H1 (SMCRUNT01)

Table 2

Protein SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
1	155	S9, S16, T25, S37, S56, S57, S81, S114, T152		G38-I73	sigma-54 interaction protein	BLOCKS
2	152	S6, T83, S103, T121, S136		H99-R112	LUPUS La protein	PRINTS
3	304	S30, S61, S94, T109, S132, S133, T183, T236, S277, S289	N65, N294	C228-C268 C231-I255	zinc finger/RING finger protein	PFAM, BLOCKS
4	178	T8, S48, S102, Y121, T144		N18-P32	histone H3 protein	PRINTS
5	301	T58, T70, T85, S148, T165, S256, T272, S281	N191	K21-F38	filaggrin structural protein	PRINTS
6	250	S99, S126, S142, S155, T182		F203-V214	maspin/breast tumor suppressor protein	PRINTS
7	371	T25, S46, S96, T123, S128, T144, S163, S167, S205, S221, T350	N203, N222, N307,N348	EQ165-Y185 K152-L192	luman/leucine zipper/CRE protein	BLAST, BLOCKS, PRINTS

Table 2 cont.

Protein SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
8	148	T35, S41, S92, S105	N144		TSC-22 transcription factor	BLAST
9	127	T69	N53	M1-E16	Ribosomal protein S6	PFAM
10	383	S22, T34, S53, S140, T155, T183, S225, T263, S273, S300, S308, T369, S375	N127	Q7-K112	PH-domain protein	Pfam
11	254	T57, S62, S92, S143, S148, T166, T176, S180, T187, S191, S194, T221			cyclin-dependent-kinase binding protein	BLAST
12	305	S65, T88, S146, S230, S248, S272	N221	G84-N271	ribosomal protein L2	PFAM, BLOCKS
13	230	T34, T49, S54, S122, T123, T150, S182, T209	N86, N130, N199	C155-C191	zinc finger/RING finger protein	PFAM, BLOCKS, MOTIFS
14	292	S2, T61, T89, T193, S223, S224, S225, S238, S288	N47, N101, N166, N259	A124-I145	FOS transforming protein	PRINTS

Table 2 cont.

Protein SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
15	232	T58, S72, S127, S149, T154, S191, S199, T203, T204	N56, N183, N187	E39-F73	tropomyosin	BLOCKS PRINTS
16	376	T5, T34, S53, T70, S81, T86, S105, S256, T287, T288, T310, S331, S364, S369, T365		Q97-C135	RecA DNA repair protein	BLOCKS BLAST
17	204	T100, T118, T157, S187, S199		L179-H200	annexin	PRINTS
18	713	S46, T64, T71, T95, S96, T129, T171, S260, S286, T345, S438, S485, T527, T541, Y567, Y593, S644, T656	N110, N453, N460, N595	L563-L576 L583-I596	RSP-1 /Ras-signaling protein	BLAST, PRINTS
19	360	S22, T51, S69, T106, S133, S206, T232, S248			Nucleolar protein Surf-6	BLAST
20	196	S38 S69 T23 T30 S73 S183 S37 T84	N9 N51	E76-L91 R35-K58	Helix-loop-helix protein HES-1	MOTIFS BLOCKS BLAST

Table 2 cont.

Protein Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
21	540	T136 S34 S69 S189 T322 S411 T7 S66 S75 T139 S193 S197 S205 T285 S324 S328 S380 S425	N240 N443	C230-H252, C260-H280, C288-H309, C316-H336, C344-H364, C372-H392, C400-H420, C428-H448, C456-H476, C484-H504, C512-H532	zinc finger protein	MOTIFS BLAST PRINTS
22	549	S123 S22 S182 T319 T465 S161 T205 S208 S332 S392 S459 S534	N167 N335 N422	C214-H234, C242-H262, C270-H290, C298-H318, C326-H346, C354-H374, C382-H402, C410-H430, C438-H458, C466-H486, C494-H514, C522-H542	zinc finger protein ZNF43	MOTIFS BLAST PRINTS
23	361	S244 T254 S8 S58 S180 S193 T269 T283 S284 T26 S45 S174 T254 S314		C139-L163 C227-K263	DNA binding protein	BLOCKS BLAST
24	241	S82 S62 S119 T147 Y111		C52-H75, C83-H105, C113-H133, C141-H161, C172-H193	zinc finger protein PZF	MOTIFS PRINTS BLAST

Table 2 cont.

Protein Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
25	576	S90 T371 S56 T183 T195 S203 S316 T318 S347 S354 S432 S548 S37 S82 S281 T325 S343 S409 S414 S447 S466 T481 S502 S570 Y323	N42 N312 N339 N498	C507-L543, L168-L189, E262-R278	transcription factor	MOTIFS PRINTS BLOCKS BLAST
26	408	S74 S197 T226 S247 T289 S328 S338 S353 S386 S394 T14 S199 S234 T388	N245 N253	G164-R175	transcription factor	PRINTS BLAST
27	810	S392 S113 S155 S185 S225 S262 S283 T298 S342 S433 T449 T665 T695 S728 T756 T801 T79 T190 S377 T438 Y397		C315-H335, C343-H363, C371-H391, C399-H419, C427-H447, C455-H475, C483-H503, C511-H531, C539-H559, C567-H587, C595-H615, C623-H644, C726-H747	zinc finger protein Miz-1	MOTIFS PRINTS BLOCKS
28	324	S72 T189 S209 T223 S279 S302 S156 T182 S316 Y277	N187	C74-R85	Hormone-binding transcription factor protein	PRINTS BLAST
29	292	S242 T41 S136 S137 T176 T200 S205 S284 T52 S61	N229	G62-S69	putative nucleotide-binding protein	MOTIFS PRINTS BLAST

Table 2 cont.

Protein Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
30	259	T79 S99 S180 T20 S152 S241		C71-H92, C43-C71	zinc finger protein	MOTIFS BLOCKS BLAST
31	97	S52		C15-L43	DNA-binding protein	MOTIFS BLOCKS BLAST
32	812	T239 T16 S55 T56 T104 S126 S127 T156 S176 T249 S268 T269 S330 T394 S450 T484 S583 S652 S658 S795 S33 S235 T314 S343 T730 S804	N45 N93 N165 N805	E418-S450	cell cycle protein	BLOCKS BLAST
33	392	T22 S30 T43 S55 S108 T140 S156 S318 T320 S343 S120 S270 S311	N277		TRAF family member-associated NF-kB activator TANK	BLAST
34	60	T49 T30 S50		I2-S55	DNA-binding protein	BLOCKS BLAST
35	209	S21 S57 T93	N67	F160-N179 S151-G185	cellular nucleic acid binding protein	PRINTS BLOCKS BLAST
36	257	T178 S187 S230 T249	N65	Y33-F44 S187-L205	cell-cycle control protein Hst2p	PRINTS BLOCKS BLAST

Table 2 cont.

Protein Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
37	138	T106 T3 S27 S46		E108-Q124	nucleic acid-binding protein	BLOCKS BLAST
38	999	T54 S634 S89 S126 S335 S414 S442 S451 T512 T762 T792 T858 S890 T97 T994 T205 S233 T274 T491 S525 S534 T577 T600 S610 S615 S634 S677 T951 S961 Y152 Y458 Y686 Y815	N43 N532 N672 N749 N818 N943	L574-L595 L647-L668	DNA-binding protein	MOTIFS BLAST
39	377	T142 T254 T48 T138 S292 S71 S74 S108 S114 T138 S222 S250 T332 T364		C130-H150, C158-H178, C186-H206, C214-H234, C242-H262, C270-H290, C296-H316, C324-H344, C352-H372	zinc finger protein ZNF132	MOTIFS PRINTS BLOCKS BLAST
40	324	S28 S214 S16 S81 S114 T225 T33 S44 T66 S203 S209 T229	N47	R26-S37 S77-L115	transcription regulatory protein IRLB	PRINTS BLOCKS BLAST
41	270	S16 T123 T141 T199 S9 S52 S90 T128 T175 S194 S214	N22 N109 N192	V218-L242 P250-Q263		MOTIFS BLOCKS PRINTS

Table 2 cont.

Protein Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
42	252	T20 S48 S89 S101 T127 S218 T121 S126 T152	N33 N46 N216 N230	Y9-L18, S68-F88, D159-S168	cell-cycle control protein	PRINTS BLAST
43	228	T50 T107 T2 S42 S201 T31 S51 T52 T103 T107 T134 T143 T206 S210 T215	N132 N141 N165 N197	A38-S51, Q65-P100, S59-K89	Transcriptional Repressor Protein	PRINTS BLOCKS BLAST
44	117	T93 T11		A86-E104	CCAAT-Binding Transcription factor	PRINTS BLAST
45	252	S83 T2 S57 T159 S250 Y102	N197	M1-S29 A85-K123	Ribosomal protein	BLOCKS MOTIFS
46	530	T177 S234 S461 S519 T24 T238	N217 N227	TM Domains: Y147-A167 Y242-L262 L306-F325 L332-L351 S379-F399 L470-F489	melibiose carrier protein	BLAST MOTIFS HMM

Table 2 cont.

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
47	355	S7 S21 T127 S213 T279 S134 T276 S315 S331 S334 Y193 Y300	N37 N192 N263 N268 N337	I42-E69 W160-E187 G171-G200 N234-I256	Mylein P0 Protein	BLOCKS, PRINTS MOTIFS, HMM
48	136	T109 S130 T5 T69 T40 S121			geminin	BLAST, MOTIFS
49	235	T138 T142 S180 S230 S111 S120 S137 T224	N140 N198	ATP/GTP binding: G9-T16	PTB-associated splicing factor	BLAST MOTIFS
50	70	T2 S64			ninjurin	BLAST MOTIFS
51	169	T128 T26 S96			B locus M Beta chain 1	BLAST, MOTIFS
52	359	S55 S78 T161 S245 T292 T350 T57 T130 T289	N105	E205-S242 E271-V294	ribosomal protein S6 kinase 2	BLAST, MOTIFS BLOCKS, PRINTS PFAM
53	545	S235 T317 S47 S73 S114 S146 S184 S236 S241 S394 S538 S2 T84 S109 S124 T230 S231 S266 S340 T360 S379 S525	N45 N139 N431 N478 N511	K88-I106 A333-K362	ribosomal protein	MOTIFS BLOCKS PRINTS

Table 2 cont.

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
54	99	T90 T43 T76			ORF E4	BLAST, MOTIFS
55	565	S27 S56 S132 T152 T197 S319 T411 T429 S475 T66 S156 S303 T390 S463 Y549	N2 N55 N165		Sec1 precursor	BLAST, MOTIFS
56	197	S65 T23 S102 S19 T60 T61 S136 S147	N20		Regulatory protein	BLAST, MOTIFS
57	321	S91 S119 T139 S283 S147 T300 Y238	N103 N194		putative ras effector Norel	BLAST, MOTIFS
58	356	T45 S85 S93 S95 T103 S114 T142 S168 T317 S340 S49 S58 T236 S258 S314 Y12 Y296	N91 N312		weak similarity to S. cerevisiae intracellular transport protein	BLAST MOTIFS
59	299	S273 T81 S116 S120 T122 S146 S86 S151 T210 S225 T268			PI3 Kinase P85 Regulator	MOTIFS, PRINTS
60	293	T34 S218 S247 S290 S291 T240 S79 S145 T156 T199 S204 S283	N152	V47-V71 K86-F93	RNA-binding protein	BLAST, MOTIFS BLOCKS, PFAM

Table 2 cont.

Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential glycosylation sites	Signature Sequence	Identification	Analytical Methods
61	777	S81 S128 S141 T230 S315 S342 S352 T519 S564 S576 S684 T699 T758 T205 S213 S236 S294 S397 T417 S470 S515 T560 S640 T746	N228 N281 N319 N453 N481 N636 N682		Zinc finger helicase	BLAST, MOTIFS
62	97	T83		C20-C28	ferredoxin	MOTIFS
63	308	S15 S81 T97 T102 S103 S135 S200 S238 S28 S131 T154 S171 S186 Y232	N58 N78 N95 N198 N236		ubiquitin-conjugating enzyme	BLAST, MOTIFS
64	290	S121 S165 S167 S248 S17 T188 T207 Y86 Y203	N55 N79	M1-A22 C60-C76 C225-C235 W249-I272	prostasin	BLAST, MOTIFS, BLO CKS, PRINTS PFAM, HMM
65	198	S7 S9 S56 T115 T34 T86	N183		transcriptional regulator	BLAST MOTIFS

TABLE 3

Nucleotide Seq ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
66	Nervous (0.256) Reproductive (0.209)	Cancer (0.442), Inflammation (0.279), Proliferative/Fetal (12%)	pBlueScript
67	Reproductive(0.274) Cardiovascular (0.194)	Cancer (0.484), Inflammation (0.145), Proliferative/Fetal (0.194)	pBlueScript
68	Reproductive (0.231) Cardiovascular (0.205)	Cancer (0.385), Inflammation (0.231), Proliferative/Fetal (0.205)	pBlueScript
69	Reproductive (0.215) Hematopoietic/Immune (0.190)	Cancer (0.397), Inflammation (0.314), Proliferative/Fetal (0.215)	pBlueScript
70	Reproductive (0.367) Cardiovascular (0.122)	Cancer (0.489), Inflammation (0.233), Proliferative/Fetal (0.189)	pBlueScript
71	Reproductive (0.292) Nervous (0.142)	Cancer (0.469), Inflammation (0.257), Proliferative/Fetal (0.177)	pSPORT1
72	Reproductive (0.261) Nervous (0.157)	Cancer (0.493), Inflammation (0.194), Trauma (0.142)	pSPORT1
73	Reproductive (0.343) Hematopoietic/Immune (0.200)	Cancer (0.457), Inflammation (0.257), Trauma (0.229)	pINCY
74	Reproductive (0.320) Nervous (0.160)	Cancer (0.507), Inflammation (0.187), Proliferative/Fetal (0.133)	pSPORT1
75	Gastrointestinal (0.300) Nervous (0.250)	Cancer (0.400), Inflammation (0.300)	pINCY
76	Reproductive (0.262) Nervous (0.180)	Cancer (0.443), Inflammation (0.262), Proliferative/Fetal (0.230)	pINCY
77	Reproductive (0.283) Nervous (0.151)	Cancer (0.509), Inflammation (0.208), Trauma (0.132)	pINCY

TABLE 3 cont.

Nucleotide Seq ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
78	Cardiovascular (0.300) Nervous (0.200)	Cancer (0.450), Inflammation (0.200)	pBlueScript
79	Reproductive (0.270) Cardiovascular (0.150)	Cancer (0.440), Inflammation (0.180), Proliferative/Fetal (0.150)	pINCY
80	Reproductive (0.271) Cardiovascular (0.153)	Cancer (0.506), Inflammation (0.176), Proliferative/Fetal (0.188)	pSPORT1
81	Hematopoietic/Immune (0.312) Reproductive (0.219)	Cancer (0.344), Inflammation (0.344), Proliferative/Fetal (0.281)	pINCY
82	Nervous (0.250) Hematopoietic/Immune (0.188)	Cancer (0.500), Inflammation (0.438), Proliferative/Fetal (0.188)	pINCY
83	Hematopoietic/Immune (0.276) Reproductive (0.276)	Cancer (0.552), Inflammation (0.310)	pINCY
84	Reproductive (0.309) Nervous (0.144)	Cancer (0.526), Inflammation (0.247), Proliferative/Fetal (0.134)	pINCY
85	Reproductive (0.315) Nervous (0.152) Cardiovascular (0.130)	Cancer (0.522) Fetal (0.174) Inflammation (0.141)	pBLUESCRIPT
86	Reproductive (0.545) Hematopeoietic/Immune (0.182) Gastrointestinal (0.182)	Cancer (0.636) Fetal (0.273) Inflammation (0.182)	pBLUESCRIPT
87	Reproductive (0.218) Nervous (0.200) Hematopoietic/Immune (0.200)	Cancer (0.509) Inflammation (0.236) Fetal (0.164)	pSPORT1
88	Nervous (0.296) Reproductive (0.185) Hematopoietic/Immune (0.148)	Cancer (0.407) Fetal (0.259) Inflammation (0.222)	pSPORT1

TABLE 3 cont.

Nucleotide Seq ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
89	Reproductive (0.339) Nervous (0.161) Gastrointestinal (0.145) Cardiovascular (0.145)	Cancer (0.613) Fetal (0.145) Inflammation (0.129)	pSPORT1
90	Cardiovascular (0.278) Gastrointestinal (0.204) Reproductive (0.185)	Cancer (0.519) Inflammation (0.204) Fetal (0.148)	pINCY
91	Reproductive (0.228) Nervous (0.149) Gastrointestinal (0.146)	Cancer (0.411) Inflammation (0.343) Fetal (0.240)	pT7T3
92	Reproductive (0.240) Hematopoietic/Immune (0.160) Gastrointestinal (0.160)	Cancer (0.460) Inflammation (0.260) Fetal (0.180)	pINCY
93	Reproductive (0.333) Cardiovascular (0.200) Hematopoietic/Immune (0.133)	Inflammation (0.533) Cancer (0.400) Fetal (0.133)	pINCY
94	Reproductive (0.230) Gastrointestinal (0.164) Cardiovascular (0.115) Hematopoietic/Immune (0.115)	Cancer (0.443) Inflammation (0.442) Fetal (0.197)	pINCY
95	Reproductive (0.333) Cardiovascular (0.167) Gastrointestinal (0.167)	Cancer (0.750) Inflammation (0.250)	pINCY
96	Reproductive (0.369) Nervous (0.215) Hematopoietic/Immune (0.108) Gastrointestinal (0.108)	Cancer (0.508) Inflammation (0.231) Fetal (0.108)	pBLUESCRIPT
97	Reproductive (0.321) Gastrointestinal (0.179) Hematopoietic/Immune (0.161)	Inflammation (0.411) Cancer (0.393) Fetal (0.161)	pINCY
98	Reproductive (0.205) Nervous (0.192) Cardiovascular (0.164)	Cancer (0.452) Inflammation (0.342) Fetal (0.178)	pSPORT1

TABLE 3 cont.

Nucleotide Seq ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
99	Gastrointestinal (0.423) Reproductive (0.115)	Cancer (0.385) Inflammation (0.288) Fetal (0.173)	pSPORT1
100	Reproductive (0.281) Hematopoietic/Immune (0.234) Nervous (0.141)	Cancer (0.375) Fetal (0.312) Inflammation (0.312)	pINCY
101	Reproductive (0.294) Nervous (0.196) Gastrointestinal (0.118)	Cancer (0.529) Fetal (0.255)	pINCY
102	Reproductive (0.217) Nervous (0.163) Cardiovascular (0.141)	Cancer (0.435) Inflammation (0.174) Fetal (0.152)	pINCY
103	Reproductive (0.263) Hematopoietic/Immune (0.158) Musculoskeletal (0.158)	Cancer (0.526) Inflammation (0.263) Fetal (0.158)	pINCY
104	Nervous (0.400) Reproductive (0.300)	Cancer (0.400) Inflammation (0.300)	pSPORT1
105	Reproductive (0.375) Cardiovascular (0.125) Urologic (0.125)	Cancer (0.500) Inflammation (0.250) Fetal (0.208)	pINCY
106	Gastrointestinal (0.400) Reproductive (0.400) Developmental (0.100) Hematopoietic/Immune (0.100)	Cancer (0.600) Fetal (0.200) Inflammation (0.200)	pINCY
107	Reproductive (0.278) Gastrointestinal (0.152) Nervous (0.139)	Cancer (0.418) Inflammation (0.241) Fetal (0.165)	>pINCY
108	Reproductive (0.364) Hematopoietic/Immune (0.182) Nervous (0.167)	Inflammation (0.409) Cancer (0.364) Fetal (0.136)	pSPORT1

TABLE 3 cont.

Nucleotide Seq ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
109	Nervous (0.227) Reproductive (0.205) Cardiovascular (0.136) Urologic (0.136) Gastrointestinal (0.136)	Cancer (0.568) Inflammation (0.182) Fetal (0.136)	pINCY
110	Hematopoietic/Immune (0.400) Urologic (0.400) Reproductive (0.200)	Cell proliferation (0.800) Inflammation (0.800)	pBluescript
111	Gastrointestinal (0.213) Hematopoietic/Immune (0.191) Nervous (0.191)	Cell proliferation (0.744) Inflammation (0.489)	pBluescript
112	Hematopoietic/Immune (0.405) Gastrointestinal (0.167) Cardiovascular (0.119)	Inflammation (0.619) Cell proliferation (0.381)	pBluescript
113	Hematopoietic/Immune (0.667) Cardiovascular (0.333)	Inflammation (1.000)	pSPORT1
114	Cardiovascular (0.412) Nervous (0.235) Musculoskeletal (0.118)	Cell proliferation (0.765) Inflammation (0.353)	pSPORT1
115	Cardiovascular (0.548) Reproductive (0.161) Developmental (0.129)	Cell proliferation (0.806) Inflammation (0.226)	pINCY
116	Reproductive (0.267) Cardiovascular (0.233) Hematopoietic/Immune (0.233)	Cell proliferation (0.467) Inflammation (0.500)	pINCY
117	Reproductive (0.400) Cardiovascular (0.167) Gastrointestinal (0.133)	Cell proliferation (0.600) Inflammation (0.267)	pINCY
118	Nervous (0.205) Reproductive (0.205) Other (0.154)	Cell proliferation (0.461) Inflammation (0.385)	pINCY
119	Reproductive (0.500) Nervous (0.167) Hematopoietic/Immune (0.167)	Cancer (0.500) Inflammation (0.167) Neurological (0.167)	pINCY

TABLE 3 cont.

Nucleotide Seq ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
120	Reproductive (0.396) Cardiovascular (0.125) Musculoskeletal (0.125)	Cell proliferation (0.750) Inflammation (0.209)	pINCY
121	Reproductive (0.248) Hematopoietic/Immune (0.194) Gastrointestinal (0.147)	Cell Proliferation (0.651) Inflammation (0.380)	pINCY
122	Nervous (0.264) Cardiovascular (0.132) Reproductive (0.132)	Cell proliferation (0.547) Inflammation (0.396)	pINCY
123	Reproductive (0.242) Nervous (0.152) Urologic (0.152)	Cell proliferation (0.788) Inflammation (0.303)	pINCY
124	Nervous (0.333) Cardiovascular (0.167) Hematopoietic/Immune (0.167)	Cell proliferation (0.667) Inflammation (0.500)	pSPORT1
125	Reproductive (0.290) Cardiovascular (0.161) Hematopoietic/Immune (0.113)	Cell proliferation (0.709) Inflammation (0.306)	pSPORT1
126	Reproductive (0.360) Nervous (0.120) Urologic (0.100)	Cell proliferation (0.680) Inflammation (0.320)	pINCY
127	Reproductive (0.364) Gastrointestinal (0.145) Nervous (0.145)	Cell proliferation (0.600) Inflammation (0.400)	pINCY
128	Cardiovascular (0.154) Gastrointestinal (0.154) Reproductive (0.154)	Cell proliferation (0.616) Inflammation (0.308)	pINCY
129	Urologic (1.000)	Cancer (1.000)	pINCY
130	Hematopoietic/Immune (0.214) Cardiovascular (0.143) Gastrointestinal (0.143)	Cell proliferation (0.428) Inflammation (0.357)	pINCY

TABLE 4

Protein SEQ ID NO:	Clone ID	Library	Library Comment
1	001106	U937NOT01	U937NOT01 Library was constructed at Stratagene (STR937207) using RNA isolated from U937 monocyte-like cell line (ATCC CRL1593) established from malignant cells obtained from the pleural effusion of a 37-year-old Caucasian male with diffuse histiocytic lymphoma.
2	004586	HMC1NOT01	HMC1NOT01 Library was constructed using RNA isolated from HMC-1 human mast cell line derived from a 52-year-old female. Patient history included mast cell leukemia. Family history included atherosclerotic coronary artery disease, a joint disorder involving multiple joints, cerebrovascular disease, and diabetes insipidus.
3	052927	FIBRNOT01	FIBRNOT01 Library was constructed at Stratagene (STR937212) using RNA isolated from the WI38 lung fibroblast cell line derived from a 3-month-old Caucasian female fetus.
4	082843	HUVESTB01	HUVESTB01 Library was constructed using RNA isolated from shear-stressed HUV-EC-C (ATCC CRL 1730), an endothelial cell line derived from the vein of a normal human umbilical.
5	322349	EOSIHET02	EOSIHET02 Library was constructed using RNA isolated from peripheral blood cells apheresed from a 48-year-old Caucasian male. Patient history included hypereosinophilia.
6	397663	PITUNOT02	PITUNOT02 Library was constructed using RNA (Clontech 6584-1) isolated from the pituitary gland of 87 male and female donors, 15 to 75 years old.
7	673766	CRBLNOT01	CRBLNOT01 Library was constructed using RNA isolated from cerebellum tissue of a 69-year-old Caucasian male, who died from chronic obstructive pulmonary disease. Patient history included heart failure, myocardial infarction, hypertension, osteoarthritis, and tobacco use.

TABLE 4 cont.

Protein SEQ ID NO:	Clone ID	Library	Library Comment
8	1504753	BRAITUT07	BRAITUT07 Library was constructed using RNA isolated from left frontal lobe tumor tissue removed from the brain of a 32-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated low grade desmoplastic neuronal neoplasm. Family history included atherosclerotic coronary artery disease .
9	1760185	PITUNOT03	PITUNOT03 Library was constructed using RNA isolated from pituitary tissue of a 46-year-old Caucasian male who died from colon cancer. Patient history included arthritis and peptic ulcer disease.
10	1805061	SINTNOT13	SINTNOT13 Library was constructed using RNA isolated from ileum tissue removed from a 25-year-old Asian female during a partial colectomy and temporary ileostomy. Pathology indicated moderately active chronic ulcerative colitis involving colonic mucosa from the distal margin to the ascending colon. Family history included hyperlipidemia, depressive disorder, malignant cervical neoplasm, and viral hepatitis A.
11	1850120	LUNGFET03	LUNGFET03 Library was constructed using RNA isolated from lung tissue removed from a Caucasian female fetus who died at 20 weeks' gestation. The mother was given seven days of erythromycin treatment for bronchitis during the first trimester.
12	1852290	LUNGFET03	
13	1944530	PITUNOT01	PITUNOT01 Library was constructed using RNA (Clontech 6584-2) isolated from the normal pituitary glands of 18 male and female Caucasian donors, 16 to 70 years old, who died from trauma.
14	2019742	CONNNOT01	CONNNOT01 Library was constructed using RNA isolated from mesentery fat tissue removed from a 71-year-old Caucasian male during a partial colectomy and permanent colostomy. Patient history included a cholecystectomy, viral hepatitis, and a hemagioma. Family history included atherosclerotic coronary artery disease, myocardial infarction, and extrinsic asthma.

TABLE 4 cont.

Protein SEQ ID NO:	Clone ID	Library	Library Comment
15	2056042	BEPINOT01	BEPINOT01 Library was constructed using RNA isolated from a bronchial epithelium (NHBE) primary cell line derived from a 54-year-old Caucasian male.
16	2398682	THP1AZT01	THP1AZT01 Library was constructed using RNA isolated from THP-1 promonocyte cells treated for three days with 0.8 micromolar 5-aza-2'-deoxycytidine. THP-1 (ATCC TIB 202) is a human promonocyte line derived from peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia.
17	2518753	BRAITUT21	BRAITUT21 Library was constructed using RNA isolated from brain tumor tissue removed from the midline frontal lobe of a 61-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated subfrontal meningothelial meningioma with no atypia. Patient history included depressive disorder; family history included cerebrovascular disease, senile dementia, hyperlipidemia, benign hypertension, atherosclerotic coronary artery disease, and congestive heart failure.
18	2709055	PONSAZT01	PONSAZT01 Library was constructed using polyA RNA isolated from diseased pons tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
19	2724537	LUNGTUT10	LUNGTUT10 Library was constructed using RNA isolated from lung tumor tissue removed from the left upper lobe of a 65-year-old Caucasian female during a segmental lung resection. Pathology indicated a metastatic grade 2 myxoid liposarcoma and metastatic grade 4 liposarcoma. Patient history included soft tissue cancer, breast cancer, and secondary lung cancer. Family history included benign hypertension.
20	025818	SPLNFET01	SPLNFET01 Library was constructed at Stratagene using RNA isolated from a pool of fetal spleen tissue. $2x10^6$ primary clones were amplified to stabilize the library for long-term storage. Amplification may significantly skew sequence abundances.

TABLE 4 cont.

Protein SEQ ID NO:	Clone ID	Library	Library Comment
21	438283	THYRNOT01	THYRNOT01 Library was constructed using RNA isolated from thyroid tissue removed from a 64-year-old Caucasian female who died from congestive heart failure.
22	619699	PGANNOT01	PGANNOT01 Library was constructed using RNA isolated from paraganglionic tumor tissue removed from the intra-abdominal region of a 46-year-old Caucasian male during exploratory laparotomy. Pathology indicated a benign paraganglioma and was associated with a grade 2 renal cell carcinoma, clear cell type, which did not penetrate the capsule. Surgical margins were negative for tumor.
23	693452	SYNORAT03	SYNORAT03 Library was constructed using RNA isolated from the wrist synovial membrane tissue of a 56-year-old female with rheumatoid arthritis.
24	839651	PROSTUT05	PROSTUT05 Library was constructed using RNA isolated from prostate tumor tissue removed from a 69-year-old Caucasian male during a radical prostatectomy. Pathology indicated adenocarcinoma (Gleason grade 3+4). Adenofibromatous hyperplasia was also present. Family history included congestive heart failure, multiple myeloma, hyperlipidemia, and rheumatoid arthritis.
25	1253545	LUNGFET03	LUNGFET03 Library was constructed using RNA isolated from lung tissue removed from a Caucasian female fetus who died at 20 weeks' gestation.
26	1425691	BEPINON01	BEPINON01 normalized bronchial epithelium library was constructed from 5.12 million independent clones from the BEPINOT01 library. RNA was made from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male. The normalization and hybridization conditions were adapted from Soares et al., PNAS (1994) 91:9228, using a longer (24-hour) reannealing hybridization period.
27	1484257	CORPNOT02	CORPNOT02 Library was constructed using RNA isolated from diseased corpus callosum tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.

TABLE 4 cont.

Protein SEQ ID NO:	Clone ID	Library	Library Comment
28	1732368	BRSTTUT08	BRSTTUT08 Library was constructed using RNA isolated from breast tumor tissue removed from a 45-year-old Caucasian female during unilateral extended simple mastectomy. Pathology indicated invasive nuclear grade 2-3 adenocarcinoma, ductal type, with 3 of 23 lymph nodes positive for metastatic disease. Greater than 50% of the tumor volume was in situ, both comedo and non-comedo types. Immunostains were positive for estrogen/progesterone receptors, and uninvolved tissue showed proliferative changes. The patient concurrently underwent a total abdominal hysterectomy. Patient history included valvuloplasty of mitral valve without replacement, rheumatic mitral insufficiency, and rheumatic heart disease. Family history included acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.
29	1870914	SKINBIT01	SKINBIT01 Library was constructed using RNA isolated from diseased skin tissue of the left lower leg. Patient history included erythema nodosum of the left lower leg.
30	1910984	CONNTUT01	CONNTUT01 Library was constructed using RNA isolated from a soft tissue tumor removed from the clival area of the skull of a 30-year-old Caucasian female. Pathology indicated chondroid chordoma with neoplastic cells reactive for keratin.
31	1943040	HIPONOT01	HIPONOT01 Library was constructed using RNA isolated from the hippocampus tissue of a 72-year-old Caucasian female who died from an intracranial bleed. Patient history included nose cancer, hypertension, and arthritis.
32	2076520	ISLTNOT01	ISLTNOT01 Library was constructed using RNA isolated from a pooled collection of pancreatic islet cells.
33	2291241	BRAINON01	BRAINON01 Library was constructed and normalized from 4.88 million independent clones from the BRAINOT03 library. RNA was made from brain tissue removed from a 26-year-old Caucasian male during cranioplasty and excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated a grade 4 oligoastrocytoma in the right fronto-parietal part of the brain.

TABLE 4 cont.

Protein SEQ ID NO:	Clone ID	Library	Library Comment
34	2329692	COLNNOT11	COLNNOT11 The COLNNOT11 library was constructed using RNA isolated from colon tissue removed from a 60-year-old Caucasian male during a left hemicolectomy.
35	2474110	THP1NOT03	THP1NOT03 Library was constructed using RNA isolated from untreated THP-1 cells (ATCC TIB 202), a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia.
36	2495790	ADRETUT05	ADRETUT05 Library was constructed using RNA isolated from adrenal tumor tissue removed from a 52-year-old Caucasian female during a unilateral adrenalectomy. Pathology indicated a pheochromocytoma.
37	2661254	ADRENOT08	ADRENOT08 pINCY Library was constructed using RNA isolated from adrenal tissue removed from a 20-year-old Caucasian male, who died from head trauma.
38	2674047	KIDNNOT19	KIDNNOT19 pINCY Library was constructed using RNA isolated from kidney tissue removed a 65-year-old Caucasian male during an exploratory laparotomy and nephroureterectomy. Pathology for the associated tumor tissue indicated a grade 1 renal cell carcinoma within the upper pole of the left kidney. Patient history included malignant melanoma of the abdominal skin, benign neoplasm of colon, cerebrovascular disease, and umbilical hernia. Family history included cardiovascular and cerebrovascular disease, and prostate cancer.

TABLE 4 cont.

Protein SEQ ID NO:	Clone ID	Library	Library Comment
39	2762174	BRAINOS12	BRAINOS12 pSPORT1 Library was constructed from 4.9 million clones from the BRAINOT03 library by subtraction of abundantly expressed clone pools. RNA was made from brain tissue removed from a 26-year-old Caucasian male during cranioplasty and excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated a grade 4 oligoastrocytoma in the right fronto-parietal part of the brain.
40	2765991	BRSTNOT12	BRSTNOT12 pINCY Library was constructed using RNA isolated from diseased breast tissue removed from a 32-year-old Caucasian female during a bilateral reduction mammoplasty. Pathology indicated nonproliferative fibrocystic disease. Family history included benign hypertension and atherosclerotic coronary artery disease.
41	2775157	PANCNOT15	PANCNOT15 pINCY Library was constructed using RNA isolated from diseased pancreatic tissue removed from a 15-year-old Caucasian male during a exploratory laparotomy with distal pancreatectomy and total splenectomy. Pathology indicated islet cell hyperplasia Family history included prostate cancer and cardiovacular disease.
42	2918375	THYMFET03	THYMFET03 Library was constructed using RNA isolated from thymus tissue removed from a Caucasian male fetus.
43	3149729	ADRENON04	ADRENON04 normalized adrenal gland library was constructed from 1.36 million independent clones from an adrenal tissue library. Starting RNA was made from adrenal gland tissue removed from a 20-year-old Caucasian male who died from head trauma. The library was normalized in two rounds using conditions adapted from Soares et al. (PNAS (1994) 91:9228-9232) and Bonaldo et al. (Genome Res (1996) 6: 791-806) and a significantly longer (48-hours/round) reannealing hybridization period.
44	3705895	PENCNOT07	PENCNOT07 Library was constructed using RNA isolated from penis right corpora cavernosa tissue removed from a male.

TABLE 4 cont.

Protein SEQ ID NO:	Clone ID	Library	Library Comment
45	003256	HMC1NOT01	HMC1NOT01 library was constructed using RNA isolated from the HMC-1 human mast cell line derived from a 52-year-old female. Patient history included mast cell leukemia.
46	156986	THP1PLB02	THP1PLB02 library was constructed by reamplification of THP1PLB01, which was made using RNA isolated from THP-1 cells cultured for 48 hours with 100 ng/ml phorbol ester (PMA), followed by a 4-hour culture in media containing 1 ug/ml LPS. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
47	319415	EOSIHET02	EOSIHET02 library was constructed using RNA isolated from peripheral blood cells apheresed from a 48-year-old Caucasian male. Patient history included hypereosinophilia. The cell population was determined to be greater than 77% eosinophils by Wright's staining.
48	635581	NEUTGMT01	NEUTGMT01 library was constructed using RNA isolated from peripheral blood granulocytes collected by density gradient centrifugation through Ficoll-Hypaque. The cells were isolated from buffy coat units obtained from 20 unrelated male and female donors. Cells were cultured in 10 nM GM-CSF for 1 hour before washing and harvesting for total RNA preparation.
49	921803	RATRNOT02	RATRNOT02 library was constructed using RNA isolated from the right atrium tissue of a 39-year-old Caucasian male, who died from a gunshot wound.
50	1250492	LUNGFET03	LUNGFET03 library was constructed using RNA isolated from lung tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation.
51	1427838	SINTBST01	SINTBST01 library was constructed using RNA isolated from ileum tissue obtained from an 18-year-old Caucasian female during bowel anastomosis. Pathology indicated Crohn's disease of the ileum, involving 15 cm of the small bowel. Family history included cerebrovascular disease and atherosclerotic coronary artery disease.

TABLE 4 cont.

Protein SEQ ID NO:	Clone ID	Library	Library Comment
52	1448258	PLACNOT02	PLACNOT02 library was constructed using RNA isolated from the placental tissue of a Hispanic female fetus, who was prematurely delivered at 21 weeks' gestation. Serologies of the mother's blood were positive for CMV (cytomegalovirus).
53	1645941	PROSTUT09	PROSTUT09 library was constructed using RNA isolated from prostate tumor tissue removed from a 66-year-old Caucasian male during a radical prostatectomy, radical cystectomy, and urinary diversion. Pathology indicated grade 3 transitional cell carcinoma. The patient presented with prostatic inflammatory disease. Patient history included lung neoplasm and benign hypertension. Family history included a malignant breast neoplasm, tuberculosis, cerebrovascular disease, atherosclerotic coronary artery disease and lung cancer.
54	1646005	PROSTUT09	PROSTUT09 library was constructed using RNA isolated from prostate tumor tissue removed from a 66-year-old Caucasian male during a radical prostatectomy, radical cystectomy, and urinary diversion. Pathology indicated grade 3 transitional cell carcinoma. The patient presented with prostatic inflammatory disease. Patient history included lung neoplasm and benign hypertension. Family history included a malignant breast neoplasm, tuberculosis, cerebrovascular disease, atherosclerotic coronary artery disease and lung cancer.
55	1686561	PROSNOT15	PROSNOT15 library was constructed using RNA isolated from diseased prostate tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 2+3). The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.

TABLE 4 cont.

Protein SEQ ID NO:	Clone ID	Library	Library Comment
56	1821233	GBLATUT01	The GBLATUT01 library was constructed using RNA isolated from gallbladder tumor tissue removed from a 78-year-old Caucasian female during a cholecystectomy. Pathology indicated invasive grade 2 squamous cell carcinoma, forming a mass in the gallbladder. Patient history included diverticulitis of the colon, palpitations, benign hypertension, and hyperlipidemia. Family history included a cholecystectomy, atherosclerotic coronary artery disease, atherosclerotic coronary artery disease, hyperlipidemia, and benign hypertension.
57	1877278	LEUKNOT03	The LEUKNOT03 library was constructed using RNA isolated from white blood cells of a 27-year-old female with blood type A+. The donor tested negative for cytomegalovirus (CMV).
58	1880692	LEUKNOT03	The LEUKNOT03 library was constructed using RNA isolated from white blood cells of a 27-year-old female with blood type A+. The donor tested negative for cytomegalovirus (CMV).
59	2280456	PROSNON01	The PROSNON01 library was constructed and normalized from 4.4 Million independent clones from the PROSNOT11 library. RNA was made from prostate tissue removed from a 28-year-old Caucasian male who died from a self-inflicted gunshot wound. The normalization and hybridization conditions were adapted from Soares, M.B. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228-9232, using a longer (19 hour) reannealing hybridization period.
60	2284580	BRAINON01	The BRAINON01 library was constructed and normalized from 4.88 million independent clones from the BRAINOT03 library. RNA was made from brain tissue removed from a 26-year-old Caucasian male during cranioplasty and excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated a grade 4 oligoastrocytoma in the right fronto-parietal part of the brain.

TABLE 4 cont.

Protein SEQ ID NO:	Clone ID	Library	Library Comment
61	2779172	OVARTUT03	OVARTUT03 library was constructed using RNA isolated from ovarian tumor tissue removed from the left ovary of a 52-year-old mixed ethnicity female during a total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal and lymphatic structure biopsy, regional lymph node excision, and peritoneal tissue destruction. Pathology indicated an invasive grade 3 (of 4) seroanaplastic carcinoma forming a mass in the left ovary. Patient history included breast cancer, chronic peptic ulcer, and joint pain. Family history included colon cancer, cerebrovascular disease, breast cancer, type II diabetes, esophagus cancer, and depressive disorder.
62	3279329	STOMFET02	STOMFET02 library was constructed using RNA isolated from stomach tissue removed from a Hispanic male fetus, who died at 18 weeks' gestation.
63	3340290	SPLNNOT10	SPLNNOT10 library was constructed using RNA isolated from spleen tissue removed from a 59-year-old Caucasian male during a total splenectomy and exploratory laparotomy. Pathology for the spleen indicated splenomegaly with congestion. The lymph nodes showed reactive follicular hyperplasia. The liver showed mild, nonspecific steatosis. The patient presented with abdominal pain, bloating of the abdomen, low-grade fever, and diaphoresis. Family history included myocardial infarction, arteriosclerotic cardiovascular disease, primary tuberculous infection, cerebrovascular disease and lymphoma.
64	3376404	PENGNOT01	PENGNOT01 library was constructed using RNA isolated from glans tissue removed from the penis of a 3-year-old Black male. Pathology for the associated tumor tissue indicated invasive grade 4 urothelial carcinoma forming a soft tissue scrotal mass that invaded the cavernous body of the penis and encased both testicles.
65	4173111	SINTNOT21	SINTNOT21 library was constructed using RNA isolated from small intestine tissue obtained from a 8-year-old Black male, who died from anoxia. Serology was negative.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	*ESTs:* Probability value= 1.0E-8 or less *Full Length sequences:* Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	*ESTs:* fasta E value=1.06E-6 *Assembled ESTs:* fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less *Full Length sequences:* fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 cont.

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Score= 4.0 or greater
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. supra; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-65, and fragments thereof.

2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.

3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.

4. An isolated and purified polynucleotide variant having at least 70% polynucleotide sequence identity to the polynucleotide of claim 3.

5. An isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide of claim 3.

6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.

7. A method for detecting a polynucleotide, the method comprising the steps of:

(a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and

(b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.

8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.

9. An isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:66-130, and fragments thereof.

10. An isolated and purified polynucleotide variant having at least 70% polynucleotide sequence identity to the polynucleotide of claim 9.

11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.

12. An expression vector comprising at least a fragment of the polynucleotide of claim 3.

13. A host cell comprising the expression vector of claim 12.

14. A method for producing a polypeptide, the method comprising the steps of:

a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and

b) recovering the polypeptide from the host cell culture.

15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.

16. A purified antibody which specifically binds to the polypeptide of claim 1.

17. A purified agonist of the polypeptide of claim 1.

18. A purified antagonist of the polypeptide of claim 1.

19. A method for treating or preventing a disorder associated with decreased expression or activity of HTRM, the method comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 15.

20. A method for treating or preventing a disorder associated with increased expression or activity of HTRM, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

SEQUENCE LISTING

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      REDDY, Roopa
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Phe His Leu Asn Thr Leu Lys Glu Ser Lys Ser Leu Trp Asp Ser
               35                   40                  45
Ala Ser Gly Gly Gly Val Val Ala Ile Asp Asn Lys Ile Glu Gln
               50                   55                  60
Ala Met Asp Leu Val Lys Ser His Leu Met Tyr Ala Val Arg Glu
               65                   70                  75
Glu Val Glu Val Leu Lys Glu Gln Ile Lys Glu Leu Val Glu Arg
               80                   85                  90
Asn Ser Leu Leu Glu Arg Glu Asn Ala Leu Leu Lys Ser Leu Ser
               95                  100                 105
Ser Asn Asp Gln Leu Ser Gln Leu Pro Thr Gln Gln Ala Asn Pro
              110                  115                 120
Gly Ser Thr Ser Gln Gln Gln Ala Val Ile Ala Gln Pro Pro Gln
```

125 130 135
Pro Thr Gln Pro Pro Gln Gln Pro Asn Val Ser Ser Ala
140 145

<210> 9
<211> 127
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1760185CD1

<400> 9
Met Arg Pro Leu Asp Ile Val Glu Leu Ala Glu Pro Glu Glu Val
1 5 10 15
Glu Val Leu Glu Pro Glu Glu Asp Phe Glu Gln Phe Leu Leu Pro
20 25 30
Val Ile Asn Glu Met Arg Glu Asp Ile Ala Ser Leu Thr Arg Glu
35 40 45
His Gly Arg Ala Tyr Leu Arg Asn Arg Ser Lys Leu Trp Glu Met
50 55 60
Asp Asn Met Leu Ile Gln Ile Lys Thr Gln Val Glu Ala Ser Glu
65 70 75
Glu Ser Ala Leu Asn His Leu Gln Asn Pro Gly Asp Ala Ala Glu
80 85 90
Gly Arg Ala Ala Lys Arg Cys Glu Lys Ala Glu Glu Lys Ala Lys
95 100 105
Glu Ile Ala Lys Met Ala Glu Met Leu Val Glu Leu Val Arg Arg
110 115 120
Ile Glu Lys Ser Glu Ser Ser
125

<210> 10
<211> 383
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1805061CD1

<400> 10
Met Pro Tyr Val Asp Arg Gln Asn Arg Ile Cys Gly Phe Leu Asp
1 5 10 15
Ile Glu Glu Asn Glu Asn Ser Gly Lys Phe Leu Arg Arg Tyr Phe
20 25 30
Ile Leu Asp Thr Arg Glu Asp Ser Phe Val Trp Tyr Met Asp Asn
35 40 45
Pro Gln Asn Leu Pro Ser Gly Ser Ser Arg Val Gly Ala Ile Lys
50 55 60
Leu Thr Tyr Ile Ser Lys Val Ser Asp Ala Thr Lys Leu Arg Pro
65 70 75
Lys Ala Glu Phe Cys Phe Val Met Asn Ala Gly Met Arg Lys Tyr
80 85 90
Phe Leu Gln Ala Asn Asp Gln Gln Asp Leu Val Glu Trp Val Asn
95 100 105

Val Leu Asn Lys Ala Ile Lys Ile Thr Val Pro Lys Gln Ser Asp
110 115
Ser Gln Pro Asn Ser Asp Asn Leu Ser Arg His Gly Glu Cys Gly
120 125 130
Lys Lys Gln Val Ser Tyr Arg Thr Asp Ile Val Gly Gly Val Pro
135 140 145
Ile Ile Thr Pro Thr Gln Lys Glu Glu Val Asn Glu Cys Gly Glu
150 155 160
Ser Ile Asp Arg Asn Asn Leu Lys Arg Ser Gln Ser His Leu Pro
165 170 175
Tyr Phe Thr Pro Lys Pro Pro Gln Asp Ser Ala Val Ile Lys Ala
180 185 190
Gly Tyr Cys Val Lys Gln Gly Ala Val Met Lys Asn Trp Lys Arg
195 200 205
Arg Tyr Phe Gln Leu Asp Glu Asn Thr Ile Gly Tyr Phe Lys Ser
210 215 220
Glu Leu Glu Lys Glu Pro Leu Arg Val Ile Pro Leu Lys Glu Val
225 230 235
His Lys Val Gln Glu Cys Lys Gln Ser Asp Ile Met Met Arg Asp
240 245 250
Asn Leu Phe Glu Ile Val Thr Thr Ser Arg Thr Phe Tyr Val Gln
255 260 265
Ala Asp Ser Pro Glu Glu Met His Ser Trp Ile Lys Ala Val Ser
270 275 280
Gly Ala Ile Val Ala Gln Arg Gly Pro Gly Arg Ser Ala Ser Ser
285 290 295
Met Arg Gln Ala Arg Arg Leu Ser Asn Pro Cys Ile Gln Arg Ser
300 305 310
Ile Pro Pro Val Leu Gln Asn Pro Asn Thr Leu Ser Val Leu Pro
315 320 325
Thr Gln Pro Pro Pro Pro His Ile Pro Gln Pro Leu Ala Ala Thr
330 335 340
Leu Trp Ser Gln Pro Leu Pro Trp Arg Ser Glu Asp Phe Thr Ser
345 350 355
Leu Leu Pro Arg Ser Ser Gln Gly Thr Ser Arg Ser Arg Leu Ser
360 365 370
Leu Gln Glu Asn Gln Leu Pro Lys
375 380

<210> 11
<211> 254
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1850120CD1

<400> 11
Met Ser Leu Ala Arg Gly His Gly Asp Thr Ala Ala Ser Thr Ala
1 5 10
Ala Pro Leu Ser Glu Glu Gly Glu Val Thr Ser Gly Leu Gln Ala
15 20 25
Leu Ala Val Glu Asp Thr Gly Gly Pro Ser Ala Ser Ala Gly Lys
30 35 40
Ala Glu Asp Glu Gly Glu Gly Gly Arg Glu Glu Thr Glu Arg Glu
45 50 55
Gly Ser Gly Gly Glu Glu Ala Gln Gly Glu Val Pro Ser Ala Gly
60 65 70
Gly Glu Glu Pro Ala Glu Glu Asp Ser Glu Asp Trp Cys Val Pro
75 80 85
Cys Ser Asp Glu Glu Val Glu Leu Pro Ala Asp Gly Gln Pro Trp
90 95 100
105

```
Met Pro Pro Pro Ser Glu Ile Gln Arg Leu Tyr Glu Leu Leu Ala
                110                 115                 120
Ala His Gly Thr Leu Glu Leu Gln Ala Glu Ile Leu Pro Arg Arg
                125                 130                 135
Pro Pro Thr Pro Glu Arg Gln Ser Glu Glu Glu Arg Ser Asp Glu
                140                 145                 150
Glu Pro Glu Ala Lys Glu Glu Glu Glu Glu Lys Pro His Met Pro
                155                 160                 165
Thr Glu Phe Asp Phe Asp Asp Glu Pro Val Thr Pro Lys Asp Ser
                170                 175                 180
Leu Ile Asp Arg Arg Arg Thr Pro Gly Ser Ser Ala Arg Ser Gln
                185                 190                 195
Lys Arg Glu Ala Arg Leu Asp Lys Val Leu Ser Asp Met Lys Arg
                200                 205                 210
His Lys Lys Leu Glu Glu Gln Ile Leu Arg Thr Gly Arg Asp Leu
                215                 220                 225
Phe Ser Leu Asp Ser Glu Asp Pro Ser Pro Ala Ser Pro Pro Leu
                230                 235                 240
Arg Ser Ser Gly Ser Ser Leu Phe Pro Arg Gln Arg Lys Tyr
                245                 250
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<210> 12
<211> 305
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1852290CD1

<400> 12

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Met Ala Leu Cys Ala Leu Thr Arg Ala Leu Arg Ser Leu Asn Leu
 1               5                  10                  15
Ala Pro Pro Thr Val Ala Ala Pro Ala Pro Ser Leu Phe Pro Ala
                20                  25                  30
Ala Gln Met Met Asn Asn Gly Leu Leu Gln Gln Pro Ser Ala Leu
                35                  40                  45
Met Leu Leu Pro Cys Arg Pro Val Leu Thr Ser Val Ala Leu Asn
                50                  55                  60
Ala Asn Phe Val Ser Trp Lys Ser Arg Thr Lys Tyr Thr Ile Thr
                65                  70                  75
Pro Val Lys Met Arg Lys Ser Gly Gly Arg Asp His Thr Gly Arg
                80                  85                  90
Ile Arg Val His Gly Ile Gly Gly Gly His Lys Gln Arg Tyr Arg
                95                 100                 105
Met Ile Asp Phe Leu Arg Phe Arg Pro Glu Glu Thr Lys Ser Gly
                110                 115                 120
Pro Phe Glu Glu Lys Val Ile Gln Val Arg Tyr Asp Pro Cys Arg
                125                 130                 135
Ser Ala Asp Ile Ala Leu Val Ala Gly Gly Ser Arg Lys Arg Trp
                140                 145                 150
Ile Ile Ala Thr Glu Asn Met Gln Ala Gly Asp Thr Ile Leu Asn
                155                 160                 165
Ser Asn His Ile Gly Arg Met Ala Val Ala Ala Arg Glu Gly Asp
                170                 175                 180
Ala His Pro Leu Gly Ala Leu Pro Val Gly Thr Leu Ile Asn Asn
                185                 190                 195
Val Glu Ser Glu Pro Gly Arg Gly Ala Gln Tyr Ile Arg Ala Ala
                200                 205                 210
Gly Thr Cys Gly Val Leu Leu Arg Lys Val Asn Gly Thr Ala Ile
                215                 220                 225
```

Ile Gln Leu Pro Ser Lys Arg Gln Met Gln Val Leu Glu Thr Cys
230 235 240
Val Ala Thr Val Gly Arg Val Ser Asn Val Asp His Asn Lys Arg
245 250 255
Val Ile Gly Lys Ala Gly Arg Asn Arg Trp Leu Gly Lys Arg Pro
260 265 270
Asn Ser Gly Arg Trp His Arg Lys Gly Gly Trp Ala Gly Arg Lys
275 280 285
Ile Arg Pro Leu Pro Pro Met Lys Ser Tyr Val Lys Leu Pro Ser
290 295 300
Ala Ser Ala Gln Ser
305

<210> 13
<211> 230
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1944530CD1

<400> 13
Met Gly Gln Gln Ile Ser Asp Gln Thr Gln Leu Val Ile Asn Lys
1 5 10 15
Leu Pro Glu Lys Val Ala Lys His Val Thr Leu Val Arg Glu Ser
20 25 30
Gly Ser Leu Thr Tyr Glu Glu Phe Leu Gly Arg Val Ala Glu Leu
35 40 45
Asn Asp Val Thr Ala Lys Val Ala Ser Gly Gln Glu Lys His Leu
50 55 60
Leu Phe Glu Val Gln Pro Gly Ser Asp Ser Ser Ala Phe Trp Lys
65 70 75
Val Val Val Arg Val Val Cys Thr Lys Ile Asn Lys Ser Ser Gly
80 85 90
Ile Val Glu Ala Ser Arg Ile Met Asn Leu Tyr Gln Phe Ile Gln
95 100 105
Leu Tyr Lys Asp Ile Thr Ser Gln Ala Ala Gly Val Leu Ala Gln
110 115 120
Ser Ser Thr Ser Glu Glu Pro Asp Glu Asn Ser Ser Ser Val Thr
125 130 135
Ser Cys Gln Ala Ser Leu Trp Met Gly Arg Val Lys Gln Leu Thr
140 145 150
Asp Glu Glu Glu Cys Cys Ile Cys Met Asp Gly Arg Ala Asp Leu
155 160 165
Ile Leu Pro Cys Ala His Ser Phe Cys Gln Lys Cys Ile Asp Lys
170 175 180
Trp Ser Asp Arg His Arg Asn Cys Pro Ile Cys Arg Leu Gln Met
185 190 195
Thr Gly Ala Asn Glu Ser Trp Val Val Ser Asp Ala Pro Thr Glu
200 205 210
Asp Asp Met Ala Asn Tyr Ile Leu Asn Met Ala Asp Glu Ala Gly
215 220 225
Gln Pro His Arg Pro
230

<210> 14
<211> 292
<212> PRT
<213> Homo sapiens

<220>

<221> misc_feature
<223> Incyte clone 2019742CB1

<400> 14
Met Ser Gly Met Glu Ala Thr Val Thr Ile Pro Ile Trp Gln Asn
1 5 10 15
Lys Pro His Gly Ala Ala Arg Ser Val Val Arg Arg Ile Gly Thr
20 25 30
Asn Leu Pro Leu Lys Pro Cys Ala Arg Ala Ser Phe Glu Thr Leu
35 40 45
Pro Asn Ile Ser Asp Leu Cys Leu Arg Asp Val Pro Pro Val Pro
50 55 60
Thr Leu Ala Asp Ile Ala Trp Ile Ala Ala Asp Glu Glu Glu Thr
65 70 75
Tyr Ala Arg Val Arg Ser Asp Thr Arg Pro Leu Arg His Thr Trp
80 85 90
Lys Pro Ser Pro Leu Ile Val Met Gln Arg Asn Ala Ser Val Pro
95 100 105
Asn Leu Arg Gly Ser Glu Glu Arg Leu Leu Ala Leu Lys Lys Pro
110 115 120
Ala Leu Pro Ala Leu Ser Arg Thr Thr Glu Leu Gln Asp Glu Leu
125 130 135
Ser His Leu Arg Ser Gln Ile Ala Lys Ile Val Ala Ala Asp Ala
140 145 150
Ala Ser Ala Ser Leu Thr Pro Asp Phe Leu Ser Pro Gly Ser Ser
155 160 165
Asn Val Ser Ser Pro Leu Pro Cys Phe Gly Ser Ser Phe His Ser
170 175 180
Thr Thr Ser Phe Val Ile Ser Asp Ile Thr Glu Glu Thr Glu Val
185 190 195
Glu Val Pro Glu Leu Pro Ser Val Pro Leu Leu Cys Ser Ala Ser
200 205 210
Pro Glu Cys Cys Lys Pro Glu His Lys Ala Ala Cys Ser Ser Ser
215 220 225
Glu Glu Asp Asp Cys Val Ser Leu Ser Lys Ala Ser Ser Phe Ala
230 235 240
Asp Met Met Gly Ile Leu Lys Asp Phe His Arg Met Lys Gln Ser
245 250 255
Gln Asp Leu Asn Arg Ser Leu Leu Lys Glu Glu Asp Pro Ala Val
260 265 270
Leu Ile Ser Glu Val Leu Arg Arg Lys Phe Ala Leu Lys Glu Glu
275 280 285
Asp Ile Ser Arg Lys Gly Asn
290

<210> 15
<211> 232
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2056042CD1

<400> 15
Met Ala Ser Ser Ala Ala Ser Ser Glu His Phe Glu Lys Leu His
1 5 10 15
Glu Ile Phe Arg Gly Leu His Glu Asp Leu Gln Gly Val Pro Glu
20 25 30
Arg Leu Leu Gly Thr Ala Gly Thr Glu Glu Lys Lys Lys Leu Ile
35 40 45
Arg Asp Phe Asp Glu Lys Gln Gln Glu Ala Asn Glu Thr Leu Ala
50 55 60

```
Glu Met Glu Glu Glu Leu Arg Tyr Ala Pro Leu Ser Phe Arg Asn
                65                  70                  75
Pro Met Met Ser Lys Leu Arg Asn Tyr Arg Lys Asp Leu Ala Lys
                80                  85                  90
Leu His Arg Glu Val Arg Ser Thr Pro Leu Thr Ala Thr Pro Gly
                95                  100                 105
Gly Arg Gly Asp Met Lys Tyr Gly Ile Tyr Ala Val Glu Asn Glu
                110                 115                 120
His Met Asn Arg Leu Gln Ser Gln Arg Ala Met Leu Leu Gln Gly
                125                 130                 135
Thr Glu Ser Leu Asn Arg Ala Thr Gln Ser Ile Glu Arg Ser His
                140                 145                 150
Arg Ile Ala Thr Glu Thr Asp Gln Ile Gly Ser Glu Ile Ile Glu
                155                 160                 165
Glu Leu Gly Glu Gln Arg Asp Gln Leu Glu Arg Thr Lys Ser Arg
                170                 175                 180
Leu Val Asn Thr Ser Glu Asn Leu Ser Lys Ser Arg Lys Ile Leu
                185                 190                 195
Arg Ser Met Ser Arg Lys Val Thr Thr Asn Lys Leu Leu Leu Ser
                200                 205                 210
Ile Ile Ile Leu Leu Glu Leu Ala Ile Leu Gly Gly Leu Val Tyr
                215                 220                 225
Tyr Lys Phe Phe Arg Ser His
                230
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<210> 16
<211> 376
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2398682CD1

<400> 16

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Met Arg Gly Lys Thr Phe Arg Phe Glu Met Gln Arg Asp Leu Val
 1               5                  10                  15
Ser Phe Pro Leu Ser Pro Ala Val Arg Val Lys Leu Val Ser Ala
                20                  25                  30
Gly Phe Gln Thr Ala Glu Glu Leu Leu Glu Val Lys Pro Ser Glu
                35                  40                  45
Leu Ser Lys Glu Val Gly Ile Ser Lys Ala Glu Ala Leu Glu Thr
                50                  55                  60
Leu Gln Ile Ile Arg Arg Glu Cys Leu Thr Asn Lys Pro Arg Tyr
                65                  70                  75
Ala Gly Thr Ser Glu Ser His Lys Lys Cys Thr Ala Leu Glu Leu
                80                  85                  90
Leu Glu Gln Glu His Thr Gln Gly Phe Ile Ile Thr Phe Cys Ser
                95                  100                 105
Ala Leu Asp Asp Ile Leu Gly Gly Gly Val Pro Leu Met Lys Thr
                110                 115                 120
Thr Glu Ile Cys Gly Ala Pro Gly Val Gly Lys Thr Gln Leu Cys
                125                 130                 135
Met Gln Leu Ala Val Asp Val Gln Ile Pro Glu Cys Phe Gly Gly
                140                 145                 150
Val Ala Gly Glu Ala Val Phe Ile Asp Thr Glu Gly Ser Phe Met
                155                 160                 165
Val Asp Arg Val Val Asp Leu Ala Thr Ala Cys Ile Gln His Leu
                170                 175                 180
Gln Leu Ile Ala Glu Lys His Lys Gly Glu Glu His Arg Lys Ala
                185                 190                 195
```

Leu Glu Asp Phe Thr Leu Asp Asn Ile Leu Ser His Ile Tyr Tyr
200 205 210
Phe Arg Cys Arg Asp Tyr Thr Glu Leu Leu Ala Gln Val Tyr Leu
215 220 225
Leu Pro Asp Phe Leu Ser Glu His Ser Lys Val Arg Leu Val Ile
230 235 240
Val Asp Gly Ile Ala Phe Pro Phe Arg His Asp Leu Asp Asp Leu
245 250 255
Ser Leu Arg Thr Arg Leu Leu Asn Gly Leu Ala Gln Gln Met Ile
260 265 270
Ser Leu Ala Asn Asn His Arg Leu Ala Val Ile Leu Thr Asn Gln
275 280 285
Met Thr Thr Lys Ile Asp Arg Asn Gln Ala Leu Leu Val Pro Ala
290 295 300
Leu Gly Glu Ser Trp Gly His Ala Ala Thr Ile Arg Leu Ile Phe
305 310 315
His Trp Asp Arg Lys Gln Arg Leu Ala Thr Leu Tyr Lys Ser Pro
320 325 330
Ser Gln Lys Glu Cys Thr Val Leu Phe Gln Ile Lys Pro Gln Gly
335 340 345
Phe Arg Asp Thr Val Val Thr Ser Ala Cys Ser Leu Gln Thr Glu
350 355 360
Gly Ser Leu Ser Thr Arg Lys Arg Ser Arg Asp Pro Glu Glu Glu
365 370 375
Leu

<210> 17
<211> 204
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2518753CD1

<400> 17
Met Ala Lys Val Gln Val Asn Asn Val Val Val Leu Asp Asn Pro
1 5 10 15
Ser Pro Phe Tyr Asn Pro Phe Gln Phe Glu Ile Thr Phe Glu Cys
20 25 30
Ile Glu Asp Leu Ser Glu Asp Leu Glu Trp Lys Ile Ile Tyr Val
35 40 45
Gly Ser Ala Glu Ser Glu Glu Tyr Asp Gln Val Leu Asp Ser Val
50 55 60
Leu Val Gly Pro Val Pro Ala Gly Arg His Met Phe Val Phe Gln
65 70 75
Ala Asp Ala Pro Asn Pro Gly Leu Ile Pro Asp Ala Asp Ala Val
80 85 90
Gly Val Thr Val Val Leu Ile Thr Cys Thr Tyr Arg Gly Gln Glu
95 100 105
Phe Ile Arg Val Gly Tyr Tyr Val Asn Asn Glu Tyr Thr Glu Thr
110 115 120
Glu Leu Arg Glu Asn Pro Pro Val Lys Pro Asp Phe Ser Lys Leu
125 130 135
Gln Arg Asn Ile Leu Ala Ser Asn Pro Arg Val Thr Arg Phe His
140 145 150
Ile Asn Trp Glu Asp Asn Thr Glu Lys Leu Glu Asp Ala Glu Ser
155 160 165
Ser Asn Pro Asn Leu Gln Ser Leu Leu Ser Thr Asp Ala Leu Pro
170 175 180
Ser Ala Ser Lys Gly Trp Ser Thr Ser Glu Asn Ser Leu Asn Val
185 190 195
Met Leu Glu Ser His Met Asp Cys Met

<210> 18
<211> 713
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2709055CD1

<400> 18
Met Tyr Leu Leu Ile Gln Met Cys Tyr His Leu Ala Leu Pro Trp
1 5 10 15
Tyr Ser Lys Tyr Phe Pro Tyr Leu Ala Leu Ile His Thr Ile Ile
20 25 30
Leu Met Ala Ser Ser Asn Phe Trp Phe Lys Tyr Pro Lys Thr Cys
35 40 45
Ser Lys Val Glu His Ser Val Ser Ile Leu Gly Lys Cys Phe Glu
50 55 60
Ser Pro Trp Thr Thr Lys Ala Leu Ser Glu Thr Ala Cys Glu Asp
65 70 75
Ser Glu Glu Asn Lys Gln Arg Ile Thr Gly Ala Gln Thr Leu Pro
80 85 90
Lys His Val Ser Thr Ser Ser Asp Glu Gly Ser Pro Ser Ala Ser
95 100 105
Thr Pro Met Ile Asn Lys Thr Gly Phe Lys Phe Ser Ala Glu Lys
110 115 120
Pro Val Ile Glu Val Pro Ser Met Thr Ile Leu Asp Lys Lys Asp
125 130 135
Gly Glu Gln Ala Lys Ala Leu Phe Glu Lys Val Arg Lys Phe Arg
140 145 150
Ala His Val Glu Asp Ser Asp Leu Ile Tyr Lys Leu Tyr Val Val
155 160 165
Gln Thr Val Ile Lys Thr Ala Lys Phe Ile Phe Ile Leu Cys Tyr
170 175 180
Thr Ala Asn Phe Val Asn Ala Ile Ser Phe Glu His Val Cys Lys
185 190 195
Pro Lys Val Glu His Leu Ile Gly Tyr Glu Val Phe Glu Cys Thr
200 205 210
His Asn Met Ala Tyr Met Leu Lys Lys Leu Leu Ile Ser Tyr Ile
215 220 225
Ser Ile Ile Cys Val Tyr Gly Phe Ile Cys Leu Tyr Thr Leu Phe
230 235 240
Trp Leu Phe Arg Ile Pro Leu Lys Glu Tyr Ser Phe Glu Lys Val
245 250 255
Arg Glu Glu Ser Ser Phe Ser Asp Ile Pro Asp Val Lys Asn Asp
260 265 270
Phe Ala Phe Leu Leu His Met Val Asp Gln Tyr Asp Gln Leu Tyr
275 280 285
Ser Lys Arg Phe Gly Val Phe Leu Ser Glu Val Ser Glu Asn Lys
290 295 300
Leu Arg Glu Ile Ser Leu Asn His Glu Trp Thr Phe Glu Lys Leu
305 310 315
Arg Gln His Ile Ser Arg Asn Ala Gln Asp Lys Gln Glu Leu His
320 325 330
Leu Phe Met Leu Ser Gly Val Pro Asp Ala Val Phe Asp Leu Thr
335 340 345
Asp Leu Asp Val Leu Lys Leu Glu Leu Ile Pro Glu Ala Lys Ile
350 355 360
Pro Ala Lys Ile Ser Gln Met Thr Asn Leu Gln Glu Leu His Leu
365 370 375
Cys His Cys Pro Ala Lys Val Glu Gln Thr Ala Phe Ser Phe Leu

380 385 390
Arg Asp His Leu Arg Cys Leu His Val Lys Phe Thr Asp Val Ala
395 400 405
Glu Ile Pro Ala Trp Val Tyr Leu Leu Lys Asn Leu Arg Glu Leu
410 415 420
Tyr Leu Ile Gly Asn Leu Asn Ser Glu Asn Asn Lys Met Ile Gly
425 430 435
Leu Glu Ser Leu Arg Glu Leu Arg His Leu Lys Ile Leu His Val
440 445 450
Lys Ser Asn Leu Thr Lys Val Pro Ser Asn Ile Thr Asp Val Ala
455 460 465
Pro His Leu Thr Lys Leu Val Ile His Asn Asp Gly Thr Lys Leu
470 475 480
Leu Val Leu Asn Ser Leu Lys Lys Met Met Asn Val Ala Glu Leu
485 490 495
Glu Leu Gln Asn Cys Glu Leu Glu Arg Ile Pro His Ala Ile Phe
500 505 510
Ser Leu Ser Asn Leu Gln Glu Leu Asp Leu Lys Ser Asn Asn Ile
515 520 525
Arg Thr Ile Glu Glu Ile Ile Ser Phe Gln His Leu Lys Arg Leu
530 535 540
Thr Cys Leu Lys Leu Trp His Asn Lys Ile Val Thr Ile Pro Pro
545 550 555
Ser Ile Thr His Val Lys Asn Leu Glu Ser Leu Tyr Phe Ser Asn
560 565 570
Asn Lys Leu Glu Ser Leu Pro Val Ala Val Phe Ser Leu Gln Lys
575 580 585
Leu Arg Cys Leu Asp Val Ser Tyr Asn Asn Ile Ser Met Ile Pro
590 595 600
Ile Glu Ile Gly Leu Leu Gln Asn Leu Gln His Leu His Ile Thr
605 610 615
Gly Asn Lys Val Asp Ile Leu Pro Lys Gln Leu Phe Lys Cys Ile
620 625 630
Lys Leu Arg Thr Leu Asn Leu Gly Gln Asn Cys Ile Thr Ser Leu
635 640 645
Pro Glu Lys Val Gly Gln Leu Ser Gln Leu Thr Gln Leu Glu Leu
650 655 660
Lys Gly Asn Cys Leu Asp Arg Leu Pro Ala Gln Leu Gly Gln Cys
665 670 675
Arg Met Leu Lys Lys Ser Gly Leu Val Val Glu Asp His Leu Phe
680 685 690
Asp Thr Leu Pro Leu Glu Val Lys Glu Ala Leu Asn Gln Asp Ile
695 700 705
Asn Ile Pro Phe Ala Asn Gly Ile
710

<210> 19
<211> 360
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2724537CD1

<400> 19
Met Ala Ser Leu Leu Ala Lys Asp Ala Tyr Leu Gln Ser Leu Ala
1 5 10 15
Lys Lys Ile Cys Ser His Ser Ala Pro Glu Gln Gln Ala Arg Thr
20 25 30
Arg Ala Gly Lys Thr Gln Gly Ser Glu Thr Ala Gly Pro Pro Lys
35 40 45
Lys Lys Arg Lys Lys Thr Gln Lys Lys Phe Arg Lys Arg Glu Glu

```
                         50                                55                                60
Lys Ala Ala Glu His Lys Ala Lys Ser Leu Gly Glu Lys Ser Pro
                         65                                70                                75
Ala Ala Ser Gly Ala Arg Arg Pro Glu Ala Ala Lys Glu Glu Ala
                         80                                85                                90
Ala Trp Ala Ser Ser Ser Ala Gly Asn Pro Ala Asp Gly Leu Ala
                         95                               100                               105
Thr Glu Pro Glu Ser Val Phe Ala Leu Asp Val Leu Arg Gln Arg
                        110                               115                               120
Leu His Glu Lys Ile Gln Glu Ala Arg Gly Gln Gly Ser Ala Lys
                        125                               130                               135
Glu Leu Ser Pro Ala Ala Leu Glu Lys Arg Arg Arg Arg Lys Gln
                        140                               145                               150
Glu Arg Asp Arg Lys Lys Arg Lys Arg Lys Glu Leu Arg Ala Lys
                        155                               160                               165
Glu Lys Ala Arg Lys Ala Glu Glu Ala Thr Glu Ala Gln Glu Val
                        170                               175                               180
Val Glu Ala Thr Pro Glu Gly Ala Cys Thr Glu Pro Arg Glu Pro
                        185                               190                               195
Pro Gly Leu Ile Phe Asn Lys Val Glu Val Ser Glu Asp Glu Pro
                        200                               205                               210
Ala Ser Lys Ala Gln Arg Arg Lys Glu Lys Arg Gln Arg Val Lys
                        215                               220                               225
Gly Asn Leu Thr Pro Leu Thr Gly Arg Asn Tyr Arg Gln Leu Leu
                        230                               235                               240
Glu Arg Leu Gln Ala Arg Gln Ser Arg Leu Asp Glu Leu Arg Gly
                        245                               250                               255
Gln Asp Glu Gly Lys Ala Gln Glu Leu Glu Ala Lys Met Lys Trp
                        260                               265                               270
Thr Asn Leu Leu Tyr Lys Ala Glu Gly Val Lys Ile Arg Asp Asp
                        275                               280                               285
Glu Arg Leu Leu Gln Glu Ala Leu Lys Arg Lys Glu Lys Arg Arg
                        290                               295                               300
Ala Gln Arg Gln Arg Arg Trp Glu Lys Arg Thr Ala Gly Val Val
                        305                               310                               315
Glu Lys Met Gln Gln Arg Gln Asp Arg Arg Arg Gln Asn Leu Arg
                        320                               325                               330
Arg Lys Lys Ala Ala Arg Ala Glu Arg Arg Leu Leu Arg Ala Arg
                        335                               340                               345
Lys Lys Gly Arg Ile Leu Pro Gln Asp Leu Glu Arg Ala Gly Leu
                        350                               355                               360
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<210> 20
<211> 196
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 025818CD1

<400> 20

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Met Pro Ala Asp Ile Met Glu Lys Asn Ser Ser Ser Pro Val Ala
  1               5                  10                  15
Ala Thr Pro Ala Ser Val Asn Thr Thr Pro Asp Lys Pro Lys Thr
                 20                  25                  30
Ala Ser Glu His Arg Lys Ser Ser Lys Pro Ile Met Glu Lys Arg
                 35                  40                  45
Arg Arg Ala Arg Ile Asn Glu Ser Leu Ser Gln Leu Lys Thr Leu
                 50                  55                  60
Ile Leu Asp Ala Leu Lys Lys Asp Ser Ser Arg His Ser Lys Leu
```

Glu Lys Ala Asp Ile Leu Glu Met Thr Val Lys His Leu Arg Asn
65 70 75
Leu Gln Arg Ala Gln Met Thr Ala Ala Leu Ser Thr Asp Pro Ser
80 85 90
Val Leu Gly Lys Tyr Arg Ala Gly Phe Ser Glu Cys Met Asn Glu
95 100 105
Val Thr Arg Phe Leu Ser Ser Pro Ser Thr Pro Ala Thr Ala Ala
110 115 120
Pro Pro Trp Ala Pro Thr Gln Cys His Leu Pro Ala Ala Pro Arg
125 130 135
Leu Arg Arg Thr Pro Cys Gly Gly Arg Gly Gly Thr Glu Gly Ala
140 145 150
Gln Ala Thr Pro Pro Pro Lys Leu Pro Asn Pro Pro Leu Phe Pro
155 160 165
Pro Asp Ser Lys Gln Glu Leu Glu Tyr Trp Glu Arg Arg Gly Leu
170 175 180
Phe
185 190 195

<210> 21
<211> 540
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 438283CD1

<400> 21
Met Leu Arg Glu Glu Ala Thr Lys Lys Ser Lys Glu Lys Glu Pro
1 5 10 15
Gly Met Ala Leu Pro Gln Gly Arg Leu Ala Phe Arg Asp Val Ala
20 25 30
Ile Glu Phe Ser Leu Glu Glu Trp Lys Cys Leu Asn Pro Ala Gln
35 40 45
Arg Ala Leu Tyr Arg Ala Val Met Leu Glu Asn Tyr Arg Asn Leu
50 55 60
Glu Phe Val Asp Ser Ser Leu Lys Ser Met Met Glu Phe Ser Ser
65 70 75
Thr Arg His Ser Asn Thr Gly Glu Val Ile His Thr Gly Thr Leu
80 85 90
Gln Arg His Lys Ser His His Ile Gly Asp Phe Cys Phe Pro Glu
95 100 105
Met Lys Lys Asp Ile His His Phe Glu Phe Gln Trp Gln Glu Val
110 115 120
Glu Arg Asn Gly His Glu Ala Pro Met Thr Lys Ile Lys Lys Leu
125 130 135
Thr Gly Ser Thr Asp Arg Ser Asp His Arg His Ala Gly Asn Lys
140 145 150
Pro Ile Lys Asp Gln Leu Gly Leu Ser Phe His Ser His Leu Pro
155 160 165
Glu Leu His Met Phe Gln Thr Lys Gly Lys Ile Ser Asn Gln Leu
170 175 180
Asp Lys Ser Ile Ser Gly Ala Ser Ser Ala Ser Glu Ser Gln Arg
185 190 195
Ile Ser Cys Arg Leu Lys Thr His Ile Ser Asn Lys Tyr Gly Lys
200 205 210
Asn Phe Leu His Ser Ser Phe Thr Gln Ile Gln Glu Ile Cys Met
215 220 225
Arg Glu Lys Pro Cys Gln Ser Asn Glu Cys Gly Lys Ala Phe Asn
230 235 240

Tyr Ser Ser Leu Leu Arg Arg His His Ile Thr His Ser Arg Glu
245 250 255
Arg Glu Tyr Lys Cys Asp Val Cys Gly Lys Ile Phe Asn Gln Lys
260 265 270
Gln Tyr Ile Val Tyr His His Arg Cys His Thr Gly Glu Lys Thr
275 280 285
Tyr Lys Cys Asn Glu Cys Gly Lys Thr Phe Thr Gln Met Ser Ser
290 295 300
Leu Val Cys His Arg Arg Leu His Thr Gly Glu Lys Pro Tyr Lys
305 310 315
Cys Asn Glu Cys Gly Lys Thr Phe Ser Glu Lys Ser Ser Leu Arg
320 325 330
Cys His Arg Arg Leu His Thr Gly Glu Lys Pro Tyr Lys Cys Asn
335 340 345
Glu Cys Gly Lys Thr Phe Gly Arg Asn Ser Ala Leu Val Ile His
350 355 360
Lys Ala Ile His Thr Gly Glu Lys Pro Tyr Lys Cys Asn Glu Cys
365 370 375
Gly Lys Thr Phe Ser Gln Lys Ser Ser Leu Gln Cys His His Ile
380 385 390
Leu His Thr Gly Glu Lys Pro Tyr Lys Cys Glu Glu Cys Asp Asn
395 400 405
Val Tyr Ile Arg Arg Ser His Leu Glu Arg His Arg Lys Ile His
410 415 420
Thr Gly Glu Gly Ser Tyr Lys Cys Lys Val Cys Asp Lys Ala Phe
425 430 435
Arg Ser Asp Ser Cys Leu Ala Asn His Thr Arg Val His Thr Gly
440 445 450
Glu Lys Pro Tyr Lys Cys Asn Lys Cys Ala Lys Val Phe Asn Gln
455 460 465
Lys Gly Ile Leu Ala Gln His Gln Arg Val His Thr Gly Glu Lys
470 475 480
Pro Tyr Lys Cys Asn Glu Cys Gly Lys Val Phe Asn Gln Lys Ala
485 490 495
Ser Leu Ala Lys His Gln Arg Val His Thr Ala Glu Lys Pro Tyr
500 505 510
Lys Cys Asn Glu Cys Gly Lys Ala Phe Thr Gly Gln Ser Thr Leu
515 520 525
Ile His His Gln Ala Ile His Gly Cys Arg Glu Thr Leu Gln Met
530 535 540

<210> 22
<211> 549
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 619699CD1

<400> 22
Met Leu Glu Asn Tyr Lys Asn Leu Ala Thr Val Gly Tyr Gln Leu
1 5 10 15
Phe Lys Pro Ser Leu Ile Ser Trp Leu Glu Gln Glu Glu Ser Arg
20 25 30
Thr Val Gln Arg Gly Asp Phe Gln Ala Ser Glu Trp Lys Val Gln
35 40 45
Leu Lys Thr Lys Glu Leu Ala Leu Gln Gln Asp Val Leu Gly Glu
50 55 60
Pro Thr Ser Ser Gly Ile Gln Met Ile Gly Ser His Asn Gly Gly
65 70 75
Glu Val Ser Asp Val Lys Gln Cys Gly Asp Val Ser Ser Glu His
80 85 90

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Ser Cys Leu Lys Thr His Val Arg Thr Gln Asn Ser Glu Asn Thr
                 95                 100                 105
Phe Glu Cys Tyr Leu Tyr Gly Val Asp Phe Leu Thr Leu His Lys
                110                 115                 120
Lys Thr Ser Thr Gly Glu Gln Arg Ser Val Phe Ser Gln Cys Gly
                125                 130                 135
Lys Ala Phe Ser Leu Asn Pro Asp Val Val Cys Gln Arg Thr Cys
                140                 145                 150
Thr Gly Glu Lys Ala Phe Asp Cys Ser Asp Ser Gly Lys Ser Phe
                155                 160                 165
Ile Asn His Ser His Leu Gln Gly His Leu Arg Thr His Asn Gly
                170                 175                 180
Glu Ser Leu His Glu Trp Lys Glu Cys Gly Arg Gly Phe Ile His
                185                 190                 195
Ser Thr Asp Leu Ala Val Arg Ile Gln Thr His Arg Ser Glu Lys
                200                 205                 210
Pro Tyr Lys Cys Lys Glu Cys Gly Lys Gly Phe Arg Tyr Ser Ala
                215                 220                 225
Tyr Leu Asn Ile His Met Gly Thr His Thr Gly Asp Asn Pro Tyr
                230                 235                 240
Glu Cys Lys Glu Cys Gly Lys Ala Phe Thr Arg Ser Cys Gln Leu
                245                 250                 255
Thr Gln His Arg Lys Thr His Thr Gly Glu Lys Pro Tyr Lys Cys
                260                 265                 270
Lys Asp Cys Gly Arg Ala Phe Thr Val Ser Ser Cys Leu Ser Gln
                275                 280                 285
His Met Lys Ile His Val Gly Glu Lys Pro Tyr Glu Cys Lys Glu
                290                 295                 300
Cys Gly Ile Ala Phe Thr Arg Ser Ser Gln Leu Thr Glu His Leu
                305                 310                 315
Lys Thr His Thr Ala Lys Asp Pro Phe Glu Cys Lys Val Cys Gly
                320                 325                 330
Lys Ser Phe Arg Asn Ser Ser Cys Leu Ser Asp His Phe Arg Ile
                335                 340                 345
His Thr Gly Ile Lys Pro Tyr Lys Cys Lys Asp Cys Gly Lys Ala
                350                 355                 360
Phe Thr Gln Asn Ser Asp Leu Thr Lys His Ala Arg Thr His Ser
                365                 370                 375
Gly Glu Arg Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala Phe Ala
                380                 385                 390
Arg Ser Ser Arg Leu Ser Glu His Thr Arg Thr His Thr Gly Glu
                395                 400                 405
Lys Pro Phe Glu Cys Val Lys Cys Gly Lys Ala Phe Ala Ile Ser
                410                 415                 420
Ser Asn Leu Ser Gly His Leu Arg Ile His Thr Gly Glu Lys Pro
                425                 430                 435
Phe Glu Cys Leu Glu Cys Gly Lys Ala Phe Thr His Ser Ser Ser
                440                 445                 450
Leu Asn Asn His Met Arg Thr His Ser Ala Lys Lys Pro Phe Thr
                455                 460                 465
Cys Met Glu Cys Gly Lys Ala Phe Lys Phe Pro Thr Cys Val Asn
                470                 475                 480
Leu His Met Arg Ile His Thr Gly Glu Lys Pro Tyr Lys Cys Lys
                485                 490                 495
Gln Cys Gly Lys Ser Phe Ser Tyr Ser Asn Ser Phe Gln Leu His
                500                 505                 510
Glu Arg Thr His Thr Gly Glu Lys Pro Tyr Glu Cys Lys Glu Cys
                515                 520                 525
Gly Lys Ala Phe Ser Ser Ser Ser Ser Phe Arg Asn His Glu Arg
                530                 535                 540
Arg His Ala Asp Glu Arg Leu Ser Ala
                545
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<210> 23
<211> 361
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 693452CD1

<400> 23

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Met Ala Asp Phe Lys Val Leu Ser Ser Gln Asp Ile Lys Trp Ala
 1               5                  10                  15
Leu His Glu Leu Lys Gly His Tyr Ala Ile Thr Arg Lys Ala Leu
                20                  25                  30
Ser Asp Ala Ile Lys Lys Trp Gln Glu Leu Ser Pro Glu Thr Ser
                35                  40                  45
Gly Lys Arg Lys Lys Arg Lys Gln Met Asn Gln Tyr Ser Tyr Ile
                50                  55                  60
Asp Phe Lys Phe Glu Gln Gly Asp Ile Lys Ile Glu Lys Arg Met
                65                  70                  75
Phe Phe Leu Glu Asn Lys Arg Arg His Cys Arg Ser Tyr Asp Arg
                80                  85                  90
Arg Ala Leu Leu Pro Ala Val Gln Gln Glu Gln Glu Phe Tyr Glu
                95                 100                 105
Gln Lys Ile Lys Glu Met Ala Glu His Glu Asp Phe Leu Leu Ala
               110                 115                 120
Leu Gln Met Asn Glu Glu Gln Tyr Gln Lys Asp Gly Gln Leu Ile
               125                 130                 135
Glu Cys Arg Cys Cys Tyr Gly Glu Phe Pro Phe Glu Glu Leu Thr
               140                 145                 150
Gln Cys Ala Asp Ala His Leu Phe Cys Lys Glu Cys Leu Ile Arg
               155                 160                 165
Tyr Ala Gln Glu Ala Val Phe Gly Ser Gly Lys Leu Glu Leu Ser
               170                 175                 180
Cys Met Glu Gly Ser Cys Thr Cys Ser Phe Pro Thr Ser Glu Leu
               185                 190                 195
Glu Lys Val Leu Pro Gln Thr Ile Leu Tyr Lys Tyr Tyr Glu Arg
               200                 205                 210
Lys Ala Glu Glu Glu Val Ala Ala Ala Tyr Ala Asp Glu Leu Val
               215                 220                 225
Arg Cys Pro Ser Cys Ser Phe Pro Ala Leu Leu Asp Ser Asp Val
               230                 235                 240
Lys Arg Phe Ser Cys Pro Asn Pro His Cys Arg Lys Glu Thr Cys
               245                 250                 255
Arg Lys Cys Gln Gly Leu Trp Lys Glu His Asn Gly Leu Thr Cys
               260                 265                 270
Glu Glu Leu Ala Glu Lys Asp Asp Ile Lys Tyr Arg Thr Ser Ile
               275                 280                 285
Glu Glu Lys Met Thr Ala Ala Arg Ile Arg Lys Cys His Lys Cys
               290                 295                 300
Gly Thr Gly Leu Ile Lys Ser Glu Gly Cys Asn Arg Met Ser Cys
               305                 310                 315
Arg Cys Gly Ala Gln Met Cys Tyr Leu Cys Arg Val Ser Ile Asn
               320                 325                 330
Gly Tyr Asp His Xaa Cys Gln Gln Ser Arg Leu Thr Gly Ala Pro
               335                 340                 345

Phe Gln Gly Val Phe Lys Met Leu Ser Met Asp Arg Leu Gln Cys
               350                 355                 360
Lys
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<210> 24
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 839651CD1

<400> 24
Met Trp Pro Ser Leu Glu Ala Leu Cys Ser Leu Phe Ala Ala Arg
1 5 10 15
Ser Thr Gly Ser Gln Ala Gln Ser Ala Pro Thr Pro Ala Trp Asp
20 25 30
Glu Asp Thr Ala Gln Ile Gly Pro Lys Arg Ile Arg Lys Ala Ala
35 40 45
Lys Arg Glu Leu Met Pro Cys Asp Phe Pro Gly Cys Gly Arg Ile
50 55 60
Phe Ser Asn Arg Gln Tyr Leu Asn His His Lys Lys Tyr Gln His
65 70 75
Ile His Gln Lys Ser Phe Ser Cys Pro Glu Pro Ala Cys Gly Lys
80 85 90
Ser Phe Asn Phe Lys Lys His Leu Lys Glu His Met Lys Leu His
95 100 105
Ser Asp Thr Arg Asp Tyr Ile Cys Glu Phe Cys Ala Arg Ser Phe
110 115 120
Arg Thr Ser Ser Asn Leu Val Ile His Arg Arg Ile His Thr Gly
125 130 135
Glu Lys Pro Leu Gln Cys Glu Ile Cys Gly Phe Thr Cys Arg Gln
140 145 150
Lys Ala Ser Leu Asn Trp His Gln Arg Lys His Ala Glu Thr Val
155 160 165
Ala Ala Leu Arg Phe Pro Cys Glu Phe Cys Gly Lys Arg Phe Glu
170 175 180
Lys Pro Asp Ser Val Ala Ala His Arg Ser Lys Ser His Pro Ala
185 190 195
Leu Leu Leu Ala Pro Gln Glu Ser Pro Ser Gly Pro Leu Glu Pro
200 205 210
Cys Pro Ser Ile Ser Ala Pro Gly Pro Leu Gly Ser Ser Glu Gly
215 220 225
Ser Arg Pro Ser Ala Ser Pro Gln Ala Pro Thr Leu Leu Pro Gln
230 235 240
Gln

<210> 25
<211> 576
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1253545CD1

<400> 25
Met Ala Lys Ala Gln Glu Thr Gly His Leu Val Met Asp Val Arg
1 5 10 15
Arg Tyr Gly Lys Ala Gly Ser Pro Glu Thr Lys Trp Ile Asp Ala
20 25 30
Thr Ser Gly Ile Tyr Asn Ser Glu Lys Ser Ser Asn Leu Ser Val
35 40 45
Thr Thr Asp Phe Ser Glu Ser Leu Gln Ser Ser Asn Ile Glu Ser

50 55 60
Lys Glu Ile Asn Gly Ile His Asp Glu Ser Asn Ala Phe Glu Ser
65 70 75
Lys Ala Ser Glu Ser Ile Ser Leu Lys Asn Leu Lys Arg Arg Ser
80 85 90
Gln Phe Phe Glu Gln Gly Ser Ser Asp Ser Val Val Pro Asp Leu
95 100 105
Pro Val Pro Thr Ile Ser Ala Pro Ser Arg Trp Val Trp Asp Gln
110 115 120
Glu Glu Glu Arg Lys Arg Gln Glu Arg Trp Gln Lys Glu Gln Asp
125 130 135
Arg Leu Leu Gln Glu Lys Tyr Gln Arg Glu Gln Glu Lys Leu Arg
140 145 150
Glu Glu Trp Gln Arg Ala Lys Gln Glu Ala Glu Arg Glu Asn Ser
155 160 165
Lys Tyr Leu Asp Glu Glu Leu Met Val Leu Ser Ser Asn Ser Met
170 175 180
Ser Leu Thr Thr Arg Glu Pro Ser Leu Ala Thr Trp Glu Ala Thr
185 190 195
Trp Ser Glu Gly Ser Lys Ser Ser Asp Arg Glu Gly Thr Arg Ala
200 205 210
Gly Glu Glu Glu Arg Arg Gln Pro Gln Glu Glu Val Val His Glu
215 220 225
Asp Gln Gly Lys Lys Pro Gln Asp Gln Leu Val Ile Glu Arg Glu
230 235 240
Arg Lys Trp Glu Gln Gln Leu Gln Glu Glu Gln Glu Gln Lys Arg
245 250 255
Leu Gln Ala Glu Ala Glu Glu Gln Lys Arg Pro Ala Glu Glu Gln
260 265 270
Lys Arg Gln Ala Glu Ile Glu Arg Glu Thr Ser Val Arg Ile Tyr
275 280 285
Gln Tyr Arg Arg Pro Val Asp Ser Tyr Asp Ile Pro Lys Thr Glu
290 295 300
Glu Ala Ser Ser Gly Phe Leu Pro Gly Asp Arg Asn Lys Ser Arg
305 310 315
Ser Thr Thr Glu Leu Asp Asp Tyr Ser Thr Asn Lys Asn Gly Asn
320 325 330
Asn Lys Tyr Leu Asp Gln Ile Gly Asn Thr Thr Ser Ser Gln Arg
335 340 345
Arg Ser Lys Lys Glu Gln Val Pro Ser Gly Ala Glu Leu Glu Arg
350 355 360
Gln Gln Ile Leu Gln Glu Met Arg Lys Arg Thr Pro Leu His Asn
365 370 375
Asp Asn Ser Trp Ile Arg Gln Arg Ser Ala Ser Val Asn Lys Glu
380 385 390
Pro Val Ser Leu Pro Gly Ile Met Arg Arg Gly Glu Ser Leu Asp
395 400 405
Asn Leu Asp Ser Pro Arg Ser Asn Ser Trp Arg Gln Pro Pro Trp
410 415 420
Leu Asn Gln Pro Thr Gly Phe Tyr Ala Ser Ser Ser Val Gln Asp
425 430 435
Phe Ser Arg Pro Gln Pro Gln Leu Val Ser Thr Ser Asn Arg Ala
440 445 450
Tyr Met Arg Asn Pro Ser Ser Ser Val Pro Pro Pro Ser Ala Gly
455 460 465
Ser Val Lys Thr Ser Thr Thr Gly Val Ala Thr Thr Gln Ser Pro
470 475 480
Thr Pro Arg Ser His Ser Pro Ser Ala Ser Gln Ser Gly Ser Gln
485 490 495
Leu Arg Asn Arg Ser Val Ser Gly Lys Arg Ile Cys Ser Tyr Cys
500 505 510
Asn Asn Ile Leu Gly Lys Gly Ala Ala Met Ile Ile Glu Ser Leu
515 520 525
Gly Leu Cys Tyr His Leu His Cys Phe Lys Cys Val Ala Cys Glu

530 535 540
Cys Asp Leu Gly Gly Ser Ser Ser Gly Ala Glu Val Arg Ile Arg
545 550 555
Asn His Gln Leu Tyr Cys Asn Asp Cys Tyr Leu Arg Phe Lys Ser
560 565 570
Gly Arg Pro Thr Ala Met
575

<210> 26
<211> 408
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1425691CD1

<400> 26
Met Pro Gly His Leu Gln Glu Gly Phe Gly Cys Val Val Thr Asn
1 5 10 15
Arg Phe Asp Gln Leu Phe Asp Asp Glu Ser Asp Pro Phe Glu Val
20 25 30
Leu Lys Ala Ala Glu Asn Lys Lys Lys Glu Ala Gly Gly Gly Gly
35 40 45
Val Gly Gly Pro Gly Ala Lys Ser Ala Ala Gln Ala Ala Ala Gln
50 55 60
Thr Asn Ser Asn Ala Ala Gly Lys Gln Leu Arg Lys Glu Ser Gln
65 70 75
Lys Asp Arg Lys Asn Pro Leu Pro Pro Ser Val Gly Val Val Asp
80 85 90
Lys Lys Glu Glu Thr Gln Pro Pro Val Ala Leu Lys Lys Glu Gly
95 100 105
Ile Arg Arg Val Gly Arg Arg Pro Asp Gln Gln Leu Gln Gly Glu
110 115 120
Gly Lys Ile Ile Asp Arg Arg Pro Glu Arg Arg Pro Pro Arg Glu
125 130 135
Arg Arg Phe Glu Lys Pro Leu Glu Glu Lys Gly Glu Gly Gly Glu
140 145 150
Phe Ser Val Asp Arg Pro Ile Ile Asp Arg Pro Ile Arg Gly Arg
155 160 165
Gly Gly Leu Gly Arg Gly Arg Gly Gly Arg Gly Arg Gly Met Gly
170 175 180
Arg Gly Asp Gly Phe Asp Ser Arg Gly Lys Arg Glu Phe Asp Arg
185 190 195
His Ser Gly Ser Asp Arg Ser Ser Phe Ser His Tyr Ser Gly Leu
200 205 210
Lys His Glu Asp Lys Arg Gly Gly Ser Gly Ser His Asn Trp Gly
215 220 225
Thr Val Lys Asp Glu Leu Thr Glu Ser Pro Lys Tyr Ile Gln Lys
230 235 240
Gln Ile Ser Tyr Asn Tyr Ser Asp Leu Asp Gln Ser Asn Val Thr
245 250 255
Glu Glu Thr Pro Glu Gly Glu Glu His His Pro Val Ala Asp Thr
260 265 270
Glu Asn Lys Glu Asn Glu Val Glu Glu Val Lys Glu Glu Gly Pro
275 280 285
Lys Glu Met Thr Leu Asp Glu Trp Lys Ala Ile Gln Asn Lys Asp
290 295 300
Arg Ala Lys Val Glu Phe Asn Ile Arg Lys Pro Asn Glu Gly Ala
305 310 315
Asp Gly Gln Trp Lys Lys Gly Phe Val Leu His Lys Ser Lys Ser
320 325 330
Glu Glu Ala His Ala Glu Asp Ser Val Met Asp His His Phe Arg

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                335                 340                      345
Lys Pro Ala Asn Asp Ile Thr Ser Gln Leu Glu Ile Asn Phe Gly
                350                 355                      360
Asp Leu Gly Arg Pro Gly Arg Gly Gly Arg Gly Gly Arg Gly Gly
                365                 370                      375
Arg Gly Arg Gly Gly Arg Pro Asn Arg Gly Ser Arg Thr Asp Lys
                380                 385                      390
Ser Ser Ala Ser Ala Pro Asp Val Asp Asp Pro Glu Ala Phe Pro
                395                 400                      405
Ala Leu Ala


&lt;210&gt; 27
&lt;211&gt; 810
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;220&gt;
&lt;221&gt; misc_feature
&lt;223&gt; Incyte clone 1484257CD1

&lt;400&gt; 27
Met Asp Phe Pro Gln His Ser Gln His Val Leu Glu Gln Leu Asn
  1             5                   10                       15
Gln Gln Arg Gln Leu Gly Leu Leu Cys Asp Cys Thr Phe Val Val
                20                  25                       30
Asp Gly Val His Phe Lys Ala His Lys Ala Val Leu Ala Ala Cys
                35                  40                       45
Ser Glu Tyr Phe Lys Met Leu Phe Val Asp Gln Lys Asp Val Val
                50                  55                       60
His Leu Asp Ile Ser Asn Ala Ala Gly Leu Gly Gln Val Leu Glu
                65                  70                       75
Phe Met Tyr Thr Ala Lys Leu Ser Leu Ser Pro Glu Asn Val Asp
                80                  85                       90
Asp Val Leu Ala Val Ala Thr Phe Leu Gln Met Gln Asp Ile Ile
                95                  100                      105
Thr Ala Cys His Ala Leu Lys Ser Leu Ala Glu Pro Ala Thr Ser
                110                 115                      120
Pro Gly Gly Asn Ala Glu Ala Leu Ala Gln Lys Val Cys Pro Val
                125                 130                      135
Pro Ser Pro Gly Gly Asp Lys Arg Ala Lys Glu Glu Lys Val Ala
                140                 145                      150
Thr Ser Thr Leu Ser Arg Leu Glu Gln Ala Gly Arg Ser Thr Pro
                155                 160                      165
Ile Gly Pro Ser Arg Asp Leu Lys Glu Glu Arg Gly Gly Gln Ala
                170                 175                      180
Gln Ser Ala Ala Ser Gly Ala Glu Gln Thr Glu Lys Ala Asp Ala
                185                 190                      195
Pro Arg Glu Pro Pro Pro Val Glu Leu Lys Pro Asp Pro Thr Ser
                200                 205                      210
Gly Met Ala Ala Ala Glu Ala Glu Ala Ala Leu Ser Glu Ser Ser
                215                 220                      225
Glu Gln Glu Met Glu Val Glu Pro Ala Arg Lys Gly Glu Glu Glu
                230                 235                      240
Gln Lys Glu Gln Glu Glu Gln Glu Glu Glu Gly Ala Gly Pro Ala
                245                 250                      255
Glu Val Lys Glu Glu Gly Ser Gln Leu Glu Asn Gly Glu Ala Pro
                260                 265                      270
Glu Glu Asn Glu Asn Glu Glu Ser Ala Gly Thr Asp Ser Gly Gln
                275                 280                      285
Glu Leu Gly Ser Glu Ala Arg Gly Leu Arg Ser Gly Thr Tyr Gly
                290                 295                      300
Asp Arg Thr Glu Ser Lys Ala Tyr Gly Ser Val Ile His Lys Cys
                305                 310                      315
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Glu Asp Cys Gly Lys Glu Phe Thr His Thr Gly Asn Phe Lys Arg
320 325 330
His Ile Arg Ile His Thr Gly Glu Lys Pro Phe Ser Cys Arg Glu
335 340 345
Cys Ser Lys Ala Phe Ser Asp Pro Ala Ala Cys Glu Ala His Glu
350 355 360
Lys Thr His Ser Pro Leu Lys Pro Tyr Gly Cys Glu Glu Cys Gly
365 370 375
Lys Ser Tyr Arg Leu Ile Ser Leu Leu Asn Leu His Lys Lys Arg
380 385 390
His Ser Gly Glu Ala Arg Tyr Arg Cys Glu Asp Cys Gly Lys Leu
395 400 405
Phe Thr Thr Ser Gly Asn Leu Lys Arg His Gln Leu Val His Ser
410 415 420
Gly Glu Lys Pro Tyr Gln Cys Asp Tyr Cys Gly Arg Ser Phe Ser
425 430 435
Asp Pro Thr Ser Lys Met Arg His Leu Glu Thr His Asp Thr Asp
440 445 450
Lys Glu His Lys Cys Pro His Cys Asp Lys Lys Phe Asn Gln Val
455 460 465
Gly Asn Leu Lys Ala His Leu Lys Ile His Ile Ala Asp Gly Pro
470 475 480
Leu Lys Cys Arg Glu Cys Gly Lys Gln Phe Thr Thr Ser Gly Asn
485 490 495
Leu Lys Arg His Leu Arg Ile His Ser Gly Glu Lys Pro Tyr Val
500 505 510
Cys Ile His Cys Gln Arg Gln Phe Ala Asp Pro Gly Ala Leu Gln
515 520 525
Arg His Val Arg Ile His Thr Gly Glu Lys Pro Cys Gln Cys Val
530 535 540
Met Cys Gly Lys Ala Phe Thr Gln Ala Ser Ser Leu Ile Ala His
545 550 555
Val Arg Gln His Thr Gly Glu Lys Pro Tyr Val Cys Glu Arg Cys
560 565 570
Gly Lys Arg Phe Val Gln Ser Ser Gln Leu Ala Asn His Ile Arg
575 580 585
His His Asp Asn Ile Arg Pro His Lys Cys Ser Val Cys Ser Lys
590 595 600
Ala Phe Val Asn Val Gly Asp Leu Ser Lys His Ile Ile Ile His
605 610 615
Thr Gly Glu Lys Pro Tyr Leu Cys Asp Lys Cys Gly Arg Gly Phe
620 625 630
Asn Arg Val Asp Asn Leu Arg Ser His Val Lys Thr Val His Gln
635 640 645
Gly Lys Ala Gly Ile Lys Ile Leu Glu Pro Glu Glu Gly Ser Glu
650 655 660
Val Ser Val Val Thr Val Asp Asp Met Val Thr Leu Ala Thr Glu
665 670 675
Ala Leu Ala Ala Thr Ala Val Thr Gln Leu Thr Val Val Pro Val
680 685 690
Gly Ala Ala Val Thr Ala Asp Glu Thr Glu Val Leu Lys Ala Glu
695 700 705
Ile Ser Lys Ala Val Lys Gln Val Gln Glu Glu Asp Pro Asn Thr
710 715 720
His Ile Leu Tyr Ala Cys Asp Ser Cys Gly Asp Lys Phe Leu Asp
725 730 735
Ala Asn Ser Leu Ala Gln His Val Arg Ile His Thr Ala Gln Ala
740 745 750
Leu Val Met Phe Gln Thr Asp Ala Asp Phe Tyr Gln Gln Tyr Gly
755 760 765
Pro Gly Gly Thr Trp Pro Ala Gly Gln Val Leu Gln Ala Gly Glu
770 775 780
Leu Val Phe Arg Pro Arg Asp Gly Ala Glu Gly Gln Pro Ala Leu
785 790 795

Ala Glu Thr Ser Pro Thr Ala Pro Glu Cys Pro Pro Pro Ala Glu
800 805 810

<210> 28
<211> 324
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1732368CD1

<400> 28
Met Asp Trp Ser Glu Val Lys Glu Glu Lys Asp Asn Leu Glu Ile
1 5 10 15
Lys Gln Glu Glu Lys Phe Val Gly Gln Cys Ile Lys Glu Glu Leu
20 25 30
Met His Gly Glu Cys Val Lys Glu Glu Lys Asp Phe Leu Lys Lys
35 40 45
Glu Ile Val Asp Asp Thr Lys Val Lys Glu Glu Pro Pro Ile Asn
50 55 60
His Pro Val Gly Cys Lys Arg Lys Leu Ala Met Ser Arg Cys Glu
65 70 75
Thr Cys Gly Thr Glu Glu Ala Lys Tyr Arg Cys Pro Arg Cys Met
80 85 90
Arg Tyr Ser Cys Ser Leu Pro Cys Val Lys Lys His Lys Ala Glu
95 100 105
Leu Thr Cys Asn Gly Val Arg Asp Lys Thr Ala Tyr Ile Ser Ile
110 115 120
Gln Gln Phe Thr Glu Met Asn Leu Leu Ser Asp Tyr Arg Phe Leu
125 130 135
Glu Asp Val Ala Arg Thr Ala Asp His Ile Ser Arg Asp Ala Phe
140 145 150
Leu Lys Arg Pro Ile Ser Asn Lys Tyr Met Tyr Phe Met Lys Asn
155 160 165
Arg Ala Arg Arg Gln Gly Ile Asn Leu Lys Leu Leu Pro Asn Gly
170 175 180
Phe Thr Lys Arg Lys Glu Asn Ser Thr Phe Phe Asp Lys Lys Lys
185 190 195
Gln Gln Phe Cys Trp His Val Lys Leu Gln Phe Pro Gln Ser Gln
200 205 210
Ala Glu Tyr Ile Glu Lys Arg Val Pro Asp Asp Lys Thr Ile Asn
215 220 225
Glu Ile Leu Lys Pro Tyr Ile Asp Pro Glu Lys Ser Asp Pro Val
230 235 240
Ile Arg Gln Arg Leu Lys Ala Tyr Ile Arg Ser Gln Thr Gly Val
245 250 255
Gln Ile Leu Met Lys Ile Glu Tyr Met Gln Gln Asn Leu Val Arg
260 265 270
Tyr Tyr Glu Leu Asp Pro Tyr Lys Ser Leu Leu Asp Asn Leu Arg
275 280 285
Asn Lys Val Ile Ile Glu Tyr Pro Thr Leu His Val Val Leu Lys
290 295 300
Gly Ser Asn Asn Asp Met Lys Val Leu His Gln Val Lys Ser Glu
305 310 315
Ser Thr Lys Asn Val Gly Asn Glu Asn
320

<210> 29
<211> 292

<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1870914CD1

<400> 29
Met Glu Glu Val Pro His Asp Cys Pro Gly Ala Asp Ser Ala Gln
1 5 10 15
Ala Gly Arg Gly Ala Ser Cys Gln Gly Cys Pro Asn Gln Arg Leu
20 25 30
Cys Ala Ser Gly Ala Gly Ala Thr Pro Asp Thr Ala Ile Glu Glu
35 40 45
Ile Lys Glu Lys Met Lys Thr Val Lys His Lys Ile Leu Val Leu
50 55 60
Ser Gly Lys Gly Gly Val Gly Lys Ser Thr Phe Ser Ala His Leu
65 70 75
Ala His Gly Leu Ala Glu Asp Glu Asn Thr Gln Ile Ala Leu Leu
80 85 90
Asp Ile Asp Ile Cys Gly Pro Ser Ile Pro Lys Ile Met Gly Leu
95 100 105
Glu Gly Glu Gln Val His Gln Ser Gly Ser Gly Trp Ser Pro Val
110 115 120
Tyr Val Glu Asp Asn Leu Gly Val Met Ser Val Gly Phe Leu Leu
125 130 135
Ser Ser Pro Asp Asp Ala Val Ile Trp Arg Gly Pro Lys Lys Asn
140 145 150
Gly Met Ile Lys Gln Phe Leu Arg Asp Val Asp Trp Gly Glu Val
155 160 165
Asp Tyr Leu Ile Val Asp Thr Pro Pro Gly Thr Ser Asp Glu His
170 175 180
Leu Ser Val Val Arg His Leu Ala Thr Ala His Ile Asp Gly Ala
185 190 195
Val Ile Ile Thr Thr Pro Gln Glu Val Ser Leu Gln Asp Val Arg
200 205 210
Lys Glu Ile Asn Phe Cys Arg Lys Val Lys Leu Pro Ile Ile Gly
215 220 225
Val Val Glu Asn Met Ser Gly Phe Ile Cys Pro Lys Cys Lys Lys
230 235 240
Glu Ser Gln Ile Phe Pro Pro Thr Thr Gly Gly Ala Glu Leu Met
245 250 255
Cys Gln Asp Leu Glu Val Pro Leu Leu Gly Arg Val Pro Leu Asp
260 265 270
Pro Leu Ile Gly Ile Gln Glu Phe Cys Asn Leu His Gln Ser Lys
275 280 285
Glu Glu Asn Leu Ile Ser Ser
290

<210> 30
<211> 259
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1910984CD1

<400> 30
Met Glu Cys His Leu Lys Thr His Tyr Lys Met Glu Tyr Lys Cys
1 5 10 15
Arg Ile Cys Gln Thr Val Lys Ala Asn Gln Leu Glu Leu Glu Thr
20 25 30

His Thr Arg Glu His Arg Leu Gly Asn His Tyr Lys Cys Asp Gln
35 40 45
Cys Gly Tyr Leu Ser Lys Thr Ala Asn Lys Leu Ile Glu His Val
50 55 60
Arg Val His Thr Gly Glu Arg Pro Phe His Cys Asp Gln Cys Ser
65 70 75
Tyr Ser Cys Thr Gly Lys Asp Asn Leu Asn Leu His Lys Lys Leu
80 85 90
Lys His Ala Pro Arg Gln Thr Phe Ser Cys Glu Glu Cys Leu Phe
95 100 105
Lys Thr Thr His Pro Phe Val Phe Ser Arg His Val Lys Lys His
110 115 120
Gln Ser Gly Asp Cys Pro Glu Glu Asp Lys Lys Gly Leu Cys Pro
125 130 135
Ala Pro Lys Glu Pro Ala Gly Pro Gly Ala Pro Leu Leu Val Val
140 145 150
Gly Ser Ser Arg Asn Leu Leu Ser Pro Leu Ser Val Met Ser Ala
155 160 165
Ser Gln Ala Leu Gln Thr Val Ala Leu Ser Ala Ala His Gly Ser
170 175 180
Ser Ser Glu Pro Asn Leu Ala Leu Lys Ala Leu Ala Phe Asn Gly
185 190 195
Ser Pro Leu Arg Phe Asp Lys Tyr Arg Asn Ser Asp Phe Ala His
200 205 210
Leu Ile Pro Leu Thr Met Leu Tyr Pro Lys Asn His Leu Asp Leu
215 220 225
Thr Phe His Pro Pro Arg Pro Gln Thr Ala Pro Pro Ser Ile Pro
230 235 240
Ser Pro Lys His Ser Phe Leu Ala Tyr Leu Gly Leu Arg Glu Arg
245 250 255
Ala Glu Thr Val

<210> 31
<211> 97
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1943040CD1

<400> 31
Met Glu His His Ser Ser His Gly Gly Arg Lys Arg Tyr Ala Cys
1 5 10 15
Gln Gly Cys Trp Lys Thr Phe His Phe Ser Leu Ala Leu Ala Glu
20 25 30
His Gln Lys Thr His Glu Lys Glu Lys Ser Tyr Ala Leu Gly Gly
35 40 45
Ala Arg Gly Pro Gln Pro Ser Thr Arg Glu Pro Arg Arg Gly Leu
50 55 60
Gly Arg Ala Val Pro Gln Arg Ala Trp Arg Ala Arg Leu Pro Pro
65 70 75
His Pro Gln Arg Arg Arg Gly Glu Pro Leu Cys Cys Pro Val Pro
80 85 90
Glu Gly Pro Leu Cys Arg Pro
95

<210> 32
<211> 812
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2076520CD1

<400> 32

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Met Ile Glu Pro Asp Gln Cys Phe Cys Arg Phe Asp Leu Thr Gly
  1             5                  10                  15
Thr Cys Asn Asp Asp Asp Cys Gln Trp Gln His Ile Gln Asp Tyr
               20                  25                  30
Thr Leu Ser Arg Lys Gln Leu Phe Gln Asp Ile Leu Ser Tyr Asn
               35                  40                  45
Leu Ser Leu Ile Gly Cys Ala Glu Thr Ser Thr Asn Glu Glu Ile
               50                  55                  60
Thr Ala Ser Ala Glu Lys Tyr Val Glu Lys Leu Phe Gly Val Asn
               65                  70                  75
Lys Asp Arg Met Ser Met Asp Gln Met Ala Val Leu Leu Val Ser
               80                  85                  90
Asn Ile Asn Glu Ser Lys Gly His Thr Pro Pro Phe Thr Thr Tyr
               95                 100                 105
Lys Asp Lys Arg Lys Trp Lys Pro Lys Phe Trp Arg Lys Pro Ile
              110                 115                 120
Ser Asp Asn Ser Phe Ser Ser Asp Glu Glu Gln Ser Thr Gly Pro
              125                 130                 135
Ile Lys Tyr Ala Phe Gln Pro Glu Asn Gln Ile Asn Val Pro Ala
              140                 145                 150
Leu Asp Thr Val Val Thr Pro Asp Asp Val Arg Tyr Phe Thr Asn
              155                 160                 165
Glu Thr Asp Asp Ile Ala Asn Leu Glu Ala Ser Val Leu Glu Asn
              170                 175                 180
Pro Ser His Val Gln Leu Trp Leu Lys Leu Ala Tyr Lys Tyr Leu
              185                 190                 195
Asn Gln Asn Glu Gly Glu Cys Ser Glu Ser Leu Asp Ser Ala Leu
              200                 205                 210
Asn Val Leu Ala Arg Ala Leu Glu Asn Asn Lys Asp Asn Pro Glu
              215                 220                 225
Ile Trp Cys His Tyr Leu Arg Leu Phe Ser Lys Arg Gly Thr Lys
              230                 235                 240
Asp Glu Val Gln Glu Met Cys Glu Thr Ala Val Glu Tyr Ala Pro
              245                 250                 255
Asp Tyr Gln Ser Phe Trp Thr Phe Leu His Leu Glu Ser Thr Phe
              260                 265                 270
Glu Glu Lys Asp Tyr Val Cys Glu Arg Met Leu Glu Phe Leu Met
              275                 280                 285
Gly Ala Ala Lys Gln Glu Thr Ser Asn Ile Leu Ser Phe Gln Leu
              290                 295                 300
Leu Glu Ala Leu Leu Phe Arg Val Gln Leu His Ile Phe Thr Gly
              305                 310                 315
Arg Cys Gln Ser Ala Leu Ala Ile Leu Gln Asn Ala Leu Lys Ser
              320                 325                 330
Ala Asn Asp Gly Ile Val Ala Glu Tyr Leu Lys Thr Ser Asp Arg
              335                 340                 345
Cys Leu Ala Trp Leu Ala Tyr Ile His Leu Ile Glu Phe Asn Ile
              350                 355                 360
Leu Pro Ser Lys Phe Tyr Asp Pro Ser Asn Asp Asn Pro Ser Arg
              365                 370                 375
Ile Val Asn Thr Glu Ser Phe Val Met Pro Trp Gln Ala Val Gln
              380                 385                 390
Asp Val Lys Thr Asn Pro Asp Met Leu Leu Ala Val Phe Glu Asp
              395                 400                 405
Ala Val Lys Ala Cys Thr Asp Glu Ser Leu Ala Val Glu Glu Arg
              410                 415                 420
Ile Glu Ala Cys Leu Pro Leu Tyr Thr Asn Met Ile Ala Leu His
              425                 430                 435
Gln Leu Leu Glu Arg Tyr Glu Ala Ala Met Glu Leu Cys Lys Ser
```

440 445 450
Leu Leu Glu Ser Cys Pro Ile Asn Cys Gln Leu Leu Glu Ala Leu
455 460 465
Val Ala Leu Tyr Leu Gln Thr Asn Gln His Asp Lys Ala Arg Ala
470 475 480
Val Trp Leu Thr Ala Phe Glu Lys Asn Pro Gln Asn Ala Glu Val
485 490 495
Phe Tyr His Met Cys Lys Phe Phe Ile Leu Gln Asn Arg Gly Asp
500 505 510
Asn Leu Leu Pro Phe Leu Arg Lys Phe Ile Ala Ser Phe Phe Lys
515 520 525
Pro Gly Phe Glu Lys Tyr Asn Asn Leu Asp Leu Phe Arg Tyr Leu
530 535 540
Leu Asn Ile Pro Gly Pro Ile Asp Ile Pro Ser Arg Leu Cys Lys
545 550 555
Gly Asn Phe Asp Asp Asp Met Phe Asn His Gln Val Pro Tyr Leu
560 565 570
Trp Leu Ile Tyr Cys Leu Cys His Pro Leu Gln Ser Ser Ile Lys
575 580 585
Glu Thr Val Glu Ala Tyr Glu Ala Ala Leu Gly Val Ala Met Arg
590 595 600
Cys Asp Ile Val Gln Lys Ile Trp Met Asp Tyr Leu Val Phe Ala
605 610 615
Asn Asn Arg Ala Ala Gly Ser Arg Asn Lys Val Gln Glu Phe Arg
620 625 630
Phe Phe Thr Asp Leu Val Asn Arg Cys Leu Val Thr Val Pro Ala
635 640 645
Arg Tyr Pro Ile Pro Phe Ser Ser Ala Asp Tyr Trp Ser Asn Tyr
650 655 660
Glu Phe His Asn Arg Val Ile Phe Phe Tyr Leu Ser Cys Val Pro
665 670 675
Lys Thr Gln His Ser Lys Thr Leu Glu Arg Phe Cys Ser Val Met
660 685 690
Pro Ala Asn Ser Gly Leu Ala Leu Arg Leu Leu Gln His Glu Trp
695 700 705
Glu Glu Ser Asn Val Gln Ile Leu Lys Leu Gln Ala Lys Met Phe
710 715 720
Thr Tyr Asn Ile Pro Thr Cys Leu Ala Thr Trp Lys Ile Ala Ile
725 730 735
Ala Ala Glu Ile Val Leu Lys Gly Gln Arg Glu Val His Arg Leu
740 745 750
Tyr Gln Arg Ala Leu Gln Lys Leu Pro Leu Cys Ala Ser Leu Trp
755 760 765
Lys Asp Gln Leu Leu Phe Glu Ala Ser Glu Gly Gly Lys Thr Asp
770 775 780
Asn Leu Arg Lys Leu Val Ser Lys Cys Gln Glu Ile Gly Val Ser
785 790 795
Leu Asn Glu Leu Leu Asn Leu Asn Ser Asn Lys Thr Glu Ser Lys
800 805 810
Asn His

<210> 33
<211> 392
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2291241CD1

<400> 33
Met Asp Ala Leu Val Glu Asp Asp Ile Cys Ile Leu Asn His Glu

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1               5                   10                  15
Lys Ala His Lys Arg Asp Thr Val Thr Pro Val Ser Ile Tyr Ser
                20                  25                  30
Gly Asp Glu Ser Val Ala Ser His Phe Ala Leu Val Thr Ala Tyr
                35                  40                  45
Glu Asp Ile Lys Lys Arg Leu Lys Asp Ser Glu Lys Glu Asn Ser
                50                  55                  60
Leu Leu Lys Lys Arg Ile Arg Phe Leu Glu Glu Lys Leu Ile Ala
                65                  70                  75
Arg Phe Glu Glu Glu Thr Ser Ser Val Gly Arg Glu Gln Val Asn
                80                  85                  90
Lys Ala Tyr His Ala Tyr Arg Glu Val Cys Ile Asp Arg Asp Asn
                95                  100                 105
Leu Lys Ser Lys Leu Asp Lys Met Asn Lys Asp Asn Ser Glu Ser
                110                 115                 120
Leu Lys Val Leu Asn Glu Gln Leu Gln Ser Lys Glu Val Glu Leu
                125                 130                 135
Leu Gln Leu Arg Thr Glu Val Glu Thr Gln Gln Val Met Arg Asn
                140                 145                 150
Leu Asn Pro Pro Ser Ser Asn Trp Glu Val Glu Lys Leu Ser Cys
                155                 160                 165
Asp Leu Lys Ile His Gly Leu Glu Gln Glu Leu Glu Leu Met Arg
                170                 175                 180
Lys Glu Cys Ser Asp Leu Lys Ile Glu Leu Gln Lys Ala Lys Gln
                185                 190                 195
Thr Asp Pro Tyr Gln Glu Asp Asn Leu Lys Ser Arg Asp Leu Gln
                200                 205                 210
Lys Leu Ser Ile Ser Ser Asp Asn Met Gln His Ala Tyr Trp Glu
                215                 220                 225
Leu Lys Arg Glu Met Ser Asn Leu His Leu Val Thr Gln Val Gln
                230                 235                 240
Ala Glu Leu Leu Arg Lys Leu Lys Thr Ser Thr Ala Ile Lys Lys
                245                 250                 255
Ala Cys Ala Pro Val Gly Cys Ser Glu Asp Leu Gly Arg Asp Ser
                260                 265                 270
Thr Lys Leu His Leu Met Asn Phe Thr Ala Thr Tyr Thr Arg His
                275                 280                 285
Pro Pro Leu Leu Pro Asn Gly Lys Ala Leu Cys His Thr Thr Ser
                290                 295                 300
Ser Pro Leu Pro Gly Asp Val Lys Val Leu Ser Glu Lys Ala Ile
                305                 310                 315
Leu Gln Ser Trp Thr Asp Asn Glu Arg Ser Ile Pro Asn Asp Gly
                320                 325                 330
Thr Cys Phe Gln Glu His Ser Ser Tyr Gly Arg Asn Ser Leu Glu
                335                 340                 345
Asp Asn Ser Trp Val Phe Pro Ser Pro Pro Lys Ser Ser Glu Thr
                350                 355                 360
Ala Phe Gly Glu Thr Lys Thr Lys Thr Leu Pro Leu Pro Asn Leu
                365                 370                 375
Pro Pro Leu His Tyr Leu Asp Gln His Asn Gln Asn Cys Leu Tyr
                380                 385                 390
Lys Asn
```

<210> 34
<211> 60
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2329692CD1

<400> 34
Met Ile Tyr Phe Phe Ile Ile Ile Val Glu Tyr Phe Tyr Gly Lys
1 5 10 15
Ile Phe Val Val Leu Ile Ile Pro Ile Lys Ile Met Pro Asn Thr
20 25 30
Lys Tyr Glu Phe Tyr Asp Val His Phe Val Leu Gly Ile Lys Arg
35 40 45
Lys Lys His Thr Ser Trp Lys Ser Val Ser Cys Phe Leu Leu Leu
50 55 60

<210> 35
<211> 209
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2474110CD1

<400> 35
Met Asp Pro Ser Asp Ile Tyr Ala Val Ile Gln Ile Pro Gly Ser
1 5 10 15
Arg Glu Phe Asp Val Ser Phe Arg Ser Ala Glu Lys Leu Ala Leu
20 25 30
Phe Leu Arg Val Tyr Glu Glu Lys Arg Glu Gln Glu Asp Cys Trp
35 40 45
Glu Asn Phe Val Val Leu Gly Arg Ser Lys Ser Ser Leu Lys Thr
50 55 60
Leu Phe Ile Leu Phe Arg Asn Glu Thr Val Asp Val Glu Asp Ile
65 70 75
Val Thr Trp Leu Lys Arg His Cys Asp Val Leu Ala Val Pro Val
80 85 90
Lys Val Thr Asp Arg Phe Gly Ile Trp Thr Gly Glu Tyr Lys Cys
95 100 105
Glu Ile Glu Leu Arg Gln Gly Glu Gly Gly Val Arg His Leu Pro
110 115 120
Gly Ala Phe Phe Leu Gly Ala Glu Arg Gly Tyr Ser Trp Tyr Lys
125 130 135
Gly Gln Pro Lys Thr Cys Phe Lys Cys Gly Ser Arg Thr His Met
140 145 150
Ser Gly Ser Cys Thr Gln Asp Arg Cys Phe Arg Cys Arg Glu Glu
155 160 165
Gly His Leu Ser Pro Tyr Cys Arg Lys Gly Ile Val Cys Asn Leu
170 175 180
Cys Gly Lys Arg Gly His Ala Phe Ala Gln Cys Pro Lys Ala Val
185 190 195
His Asn Ser Val Ala Ala Gln Leu Thr Gly Val Ala Gly His
200 205

<210> 36
<211> 257
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2495790CD1

<400> 36
Met Val Gly Ala Gly Ile Ser Thr Pro Ser Gly Ile Pro Asp Phe
1 5 10 15

Arg Ser Pro Gly Ser Gly Leu Tyr Ser Asn Leu Gln Gln Tyr Asp
20 25 30
Leu Pro Tyr Pro Glu Ala Ile Phe Glu Leu Pro Phe Phe Phe His
35 40 45
Asn Pro Lys Pro Phe Phe Thr Leu Ala Lys Glu Leu Tyr Pro Gly
50 55 60
Asn Tyr Lys Pro Asn Val Thr His Tyr Phe Leu Arg Leu Leu His
65 70 75
Asp Lys Gly Leu Leu Leu Arg Leu Tyr Thr Gln Asn Ile Asp Gly
80 85 90
Leu Glu Arg Val Ser Gly Ile Pro Ala Ser Lys Leu Val Glu Ala
95 100 105
His Gly Thr Phe Ala Ser Ala Thr Cys Thr Val Cys Gln Arg Pro
110 115 120
Phe Pro Gly Glu Asp Ile Arg Ala Asp Val Met Ala Asp Arg Val
125 130 135
Pro Arg Cys Pro Val Cys Thr Gly Val Val Lys Pro Asp Ile Val
140 145 150
Phe Phe Gly Glu Pro Leu Pro Gln Arg Phe Leu Leu His Val Val
155 160 165
Asp Phe Pro Met Ala Asp Leu Leu Leu Ile Leu Gly Thr Ser Leu
170 175 180
Glu Val Glu Pro Phe Ala Ser Leu Thr Glu Ala Val Arg Ser Ser
185 190 195
Val Pro Arg Leu Leu Ile Asn Arg Asp Leu Val Gly Pro Leu Ala
200 205 210
Trp His Pro Arg Ser Arg Asp Val Ala Gln Leu Gly Asp Val Val
215 220 225
His Gly Val Glu Ser Leu Val Glu Leu Leu Gly Trp Thr Glu Glu
230 235 240
Met Arg Asp Leu Val Gln Arg Glu Thr Gly Lys Leu Asp Gly Pro
245 250 255
Asp Lys

<210> 37
<211> 136
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2661254CD1

<400> 37
Met Ala Thr Lys Arg Leu Phe Gly Ala Thr Arg Thr Trp Ala Gly
1 5 10 15
Trp Gly Ala Trp Glu Leu Leu Asn Pro Ala Thr Ser Gly Arg Leu
20 25 30
Leu Ala Arg Asp Tyr Ala Lys Lys Pro Val Met Lys Gly Ala Lys
35 40 45
Ser Gly Lys Gly Ala Val Thr Ser Glu Ala Leu Lys Asp Pro Asp
50 55 60
Val Cys Thr Asp Pro Val Gln Leu Thr Thr Tyr Ala Met Gly Val
65 70 75
Asn Ile Tyr Lys Glu Gly Gln Asp Val Pro Leu Lys Pro Asp Ala
80 85 90
Glu Tyr Pro Glu Trp Leu Phe Glu Met Asn Leu Gly Pro Pro Lys
95 100 105
Thr Leu Glu Glu Leu Asp Pro Glu Ser Arg Glu Tyr Trp Arg Arg
110 115 120
Leu Arg Lys Gln Asn Ile Trp Arg His Asn Arg Leu Ser Lys Asn
125 130 135

Lys Arg Leu

<210> 38
<211> 999
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2674047CD1

<400> 38
Met Gly Pro Ser Arg Leu Arg Leu Gly Phe Phe Xaa Lys Arg Gly
1 5 10 15
Cys Ser Arg Ala Met Val Glu Ile Glu Leu Phe Arg Ala Ser Gly
20 25 30
Asn Leu Val Ile Thr Arg Glu Ile Asp Val Ala Lys Asn Gln Ser
35 40 45
Phe Trp Phe Ile Asn Lys Lys Ser Thr Thr Gln Xaa Ile Val Glu
50 55 60
Glu Lys Val Ala Ala Leu Asn Ile Gln Val Gly Asn Leu Cys Gln
65 70 75
Phe Leu Pro Gln Asp Lys Val Gly Glu Phe Ala Lys Leu Ser Lys
80 85 90
Ile Glu Leu Leu Glu Ala Thr Glu Lys Ser Ile Gly Pro Pro Glu
95 100 105
Met His Lys Tyr His Cys Glu Leu Lys Asn Leu Arg Glu Lys Glu
110 115 120
Lys Gln Leu Glu Thr Ser Cys Lys Glu Lys Thr Glu Tyr Leu Gln
125 130 135
Lys Met Val Gln Arg Asn Glu Arg Tyr Lys Gln Asp Val Glu Arg
140 145 150
Phe Tyr Glu Arg Lys Arg His Leu Asp Leu Ile Glu Met Leu Glu
155 160 165
Ala Lys Arg Pro Trp Val Glu Tyr Glu Asn Val Arg Gln Glu Tyr
170 175 180
Glu Glu Val Lys Leu Val Arg Asp Arg Val Lys Glu Glu Val Arg
185 190 195
Lys Leu Lys Glu Gly Gln Ile Pro Ile Thr Cys Arg Ile Glu Glu
200 205 210
Met Glu Asn Glu Arg His Asn Leu Glu Ala Arg Ile Lys Glu Lys
215 220 225
Ala Thr Asp Ile Lys Glu Ala Ser Gln Lys Cys Lys Gln Lys Gln
230 235 240
Asp Val Ile Glu Arg Lys Asp Lys His Ile Glu Glu Leu Gln Gln
245 250 255
Ala Leu Ile Val Lys Gln Asn Glu Glu Leu Asp Arg Gln Arg Arg
260 265 270
Ile Gly Asn Thr Arg Lys Met Ile Glu Asp Leu Gln Asn Glu Leu
275 280 285
Lys Thr Thr Glu Asn Cys Glu Asn Leu Gln Pro Gln Ile Asp Ala
290 295 300
Ile Thr Asn Asp Leu Arg Arg Ile Gln Asp Glu Lys Ala Leu Cys
305 310 315
Glu Gly Glu Ile Ile Asp Lys Arg Arg Glu Arg Glu Thr Leu Glu
320 325 330
Lys Glu Lys Lys Ser Val Asp Asp His Ile Val Arg Phe Asp Asn
335 340 345
Leu Met Asn Gln Lys Glu Asp Lys Leu Arg Gln Arg Phe Arg Asp
350 355 360
Thr Tyr Asp Ala Val Leu Trp Leu Arg Asn Asn Arg Asp Lys Phe
365 370 375

```
Lys Gln Arg Val Cys Glu Pro Ile Met Leu Thr Ile Asn Met Lys
                380                 385                 390
Asp Asn Lys Asn Ala Lys Tyr Ile Glu Asn His Ile Pro Ser Asn
                395                 400                 405
Asp Leu Arg Ala Phe Val Phe Glu Ser Gln Glu Asp Met Glu Val
                410                 415                 420
Phe Leu Lys Glu Val Arg Asp Asn Lys Lys Leu Arg Val Asn Ala
                425                 430                 435
Val Ile Ala Pro Lys Ser Ser Tyr Ala Asp Lys Ala Pro Ser Arg
                440                 445                 450
Ser Leu Asn Glu Leu Lys Gln Tyr Gly Phe Phe Ser Tyr Leu Arg
                455                 460                 465
Glu Leu Phe Asp Ala Pro Asp Pro Val Met Ser Tyr Leu Cys Cys
                470                 475                 480
Gln Tyr His Ile His Glu Val Pro Val Gly Thr Glu Lys Thr Arg
                485                 490                 495
Glu Arg Ile Glu Arg Val Ile Gln Glu Thr Arg Leu Lys Gln Ile
                500                 505                 510
Tyr Thr Ala Glu Glu Lys Tyr Val Val Lys Thr Ser Phe Tyr Ser
                515                 520                 525
Asn Lys Val Ile Ser Ser Asn Thr Ser Leu Lys Val Ala Gln Phe
                530                 535                 540
Leu Thr Val Thr Val Asp Leu Glu Gln Arg Arg His Leu Glu Glu
                545                 550                 555
Gln Leu Lys Glu Ile His Arg Lys Leu Gln Ala Val Asp Ser Gly
                560                 565                 570
Leu Ile Ala Leu Arg Glu Thr Ser Lys His Leu Glu His Lys Asp
                575                 580                 585
Asn Glu Leu Arg Gln Lys Lys Lys Glu Leu Leu Glu Arg Lys Thr
                590                 595                 600
Lys Lys Arg Gln Leu Glu Gln Lys Ile Ser Ser Lys Leu Gly Ser
                605                 610                 615
Leu Lys Leu Met Glu Gln Asp Thr Cys Asn Leu Glu Glu Glu Glu
                620                 625                 630
Arg Lys Ala Ser Thr Lys Ile Lys Glu Ile Asn Val Gln Lys Ala
                635                 640                 645
Lys Leu Val Thr Glu Leu Thr Asn Leu Ile Lys Ile Cys Thr Ser
                650                 655                 660
Leu His Ile Gln Lys Val Asp Leu Ile Leu Gln Asn Thr Thr Val
                665                 670                 675
Ile Ser Glu Lys Asn Lys Leu Glu Ser Asp Tyr Met Ala Ala Ser
                680                 685                 690
Ser Gln Leu Arg Leu Thr Glu Gln His Phe Ile Glu Leu Asp Glu
                695                 700                 705
Asn Arg Gln Arg Leu Leu Gln Lys Cys Lys Glu Leu Met Lys Arg
                710                 715                 720
Ala Arg Gln Val Cys Asn Leu Gly Ala Glu Gln Thr Leu Pro Gln
                725                 730                 735
Glu Tyr Gln Thr Gln Val Pro Thr Ile Pro Asn Gly His Asn Ser
                740                 745                 750
Ser Leu Pro Met Val Phe Gln Asp Leu Pro Asn Thr Leu Asp Glu
                755                 760                 765
Ile Asp Ala Leu Leu Thr Glu Glu Arg Ser Arg Ala Ser Cys Phe
                770                 775                 780
Thr Gly Leu Asn Pro Thr Ile Val Gln Glu Tyr Thr Lys Arg Glu
                785                 790                 795
Glu Glu Ile Glu Gln Leu Thr Glu Glu Leu Lys Gly Lys Lys Val
                800                 805                 810
Glu Leu Asp Gln Tyr Arg Glu Asn Ile Ser Gln Val Lys Glu Arg
                815                 820                 825
Trp Leu Asn Pro Leu Lys Glu Leu Val Glu Lys Ile Asn Glu Lys
                830                 835                 840
Phe Ser Asn Phe Phe Ser Ser Met Gln Cys Ala Gly Glu Val Asp
                845                 850                 855
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Leu His Thr Glu Asn Glu Glu Asp Tyr Asp Lys Tyr Gly Ile Arg
                860                 865                 870
Ile Arg Val Lys Phe Arg Ser Ser Thr Gln Leu His Glu Leu Thr
                875                 880                 885
Pro His His Gln Ser Gly Gly Glu Arg Ser Val Ser Thr Met Leu
                890                 895                 900
Tyr Leu Met Ala Leu Gln Glu Leu Asn Arg Cys Pro Phe Arg Val
                905                 910                 915
Val Asp Glu Ile Asn Gln Gly Met Asp Pro Ile Asn Glu Arg Arg
                920                 925                 930
Val Phe Glu Met Val Val Asn Thr Ala Cys Lys Glu Asn Thr Ser
                935                 940                 945
Gln Tyr Phe Phe Ile Thr Pro Lys Leu Leu Gln Asn Leu Pro Tyr
                950                 955                 960
Ser Glu Lys Met Thr Val Leu Phe Val Tyr Asn Gly Pro His Met
                965                 970                 975
Leu Glu Pro Asn Thr Trp Asn Leu Lys Ala Phe Gln Arg Arg Arg
                980                 985                 990
Arg Arg Ile Thr Phe Thr Gln Pro Ser
                995


<210> 39
<211> 377
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2762174CD1

<400> 39
Met Ala Glu Leu Glu Ser His Pro Cys Asp Ile Cys Gly Pro Ile
  1               5                  10                  15
Leu Lys Asp Thr Leu His Leu Ala Lys Tyr His Gly Gly Lys Ala
                 20                  25                  30
Arg Gln Lys Pro Tyr Leu Cys Gly Ala Cys Gly Lys Gln Phe Trp
                 35                  40                  45
Phe Ser Thr Asp Phe Asp Gln His Gln Asn Gln Pro Asn Gly Gly
                 50                  55                  60
Lys Leu Phe Pro Arg Lys Glu Gly Arg Asp Ser Val Lys Ser Cys
                 65                  70                  75
Arg Val His Val Pro Glu Lys Thr Leu Thr Cys Gly Lys Gly Arg
                 80                  85                  90
Arg Asp Phe Ser Ala Thr Ser Gly Leu Leu Gln His Gln Ala Ser
                 95                 100                 105
Leu Ser Ser Met Lys Pro His Lys Ser Thr Lys Leu Val Ser Gly
                110                 115                 120
Phe Leu Met Gly Gln Arg Tyr His Arg Cys Gly Glu Cys Gly Lys
                125                 130                 135
Ala Phe Thr Arg Lys Asp Thr Leu Ala Arg His Gln Arg Ile His
                140                 145                 150
Thr Gly Glu Arg Pro Tyr Glu Cys Asn Glu Cys Gly Lys Phe Phe
                155                 160                 165
Ser Gln Ser Tyr Asp Leu Phe Lys His Gln Thr Val His Thr Gly
                170                 175                 180
Glu Arg Pro Tyr Glu Cys Ser Glu Cys Gly Lys Phe Phe Arg Gln
                185                 190                 195
Ile Ser Gly Leu Ile Glu His Arg Arg Val His Thr Gly Glu Arg
                200                 205                 210
Leu Tyr Gln Cys Gly Lys Cys Gly Lys Phe Phe Ser Ser Lys Ser
                215                 220                 225
Asn Leu Ile Arg His Gln Glu Val His Thr Gly Ala Arg Pro Tyr
                230                 235                 240
```

Val Cys Ser Glu Cys Gly Lys Glu Phe Ser Arg Lys His Thr Leu
245 250 255
Val Leu His Gln Arg Thr His Thr Gly Glu Arg Pro Tyr Glu Cys
260 265 270
Ser Glu Cys Gly Lys Ala Phe Ser Gln Ser Ser His Leu Asn Val
275 280 285
His Trp Arg Ile His Ser Ser Asp Tyr Glu Cys Ser Arg Cys Gly
290 295 300
Lys Ala Phe Ser Cys Ile Ser Lys Leu Ile Gln His Gln Lys Val
305 310 315
His Ser Gly Glu Lys Pro Tyr Glu Cys Ser Lys Cys Gly Lys Ala
320 325 330
Phe Thr Gln Arg Pro Asn Leu Ile Arg His Trp Lys Val His Thr
335 340 345
Gly Glu Arg Pro Tyr Val Cys Ser Glu Cys Gly Arg Glu Phe Ile
350 355 360
Arg Lys Gln Thr Leu Val Leu His Gln Arg Val His Ala Gly Glu
365 370 375
Lys Leu

<210> 40
<211> 324
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2765991CD1

<400> 40
Met Asp Phe Pro Lys His Asn Gln Ile Ile Thr Glu Glu Thr Gly
1 5 10 15
Ser Ala Val Glu Pro Ser Asp Glu Ile Lys Arg Ala Ser Gly Asp
20 25 30
Val Gln Thr Met Lys Ile Ser Ser Val Pro Asn Ser Leu Ser Lys
35 40 45
Arg Asn Val Ser Leu Thr Arg Ser His Ser Val Gly Gly Pro Leu
50 55 60
Gln Asn Ile Asp Phe Thr Gln Arg Pro Phe His Gly Ile Ser Thr
65 70 75
Val Ser Leu Pro Gly Ser Leu Gln Glu Val Val Asp Pro Leu Gly
80 85 90
Lys Arg Pro Asn Pro Pro Pro Val Ser Val Pro Tyr Leu Ser Pro
95 100 105
Leu Val Leu Arg Lys Glu Leu Glu Ser Leu Leu Glu Asn Glu Gly
110 115 120
Asp Gln Val Ile His Thr Ser Ser Phe Ile Asn Gln His Pro Ile
125 130 135
Ile Phe Trp Asn Leu Val Trp Tyr Phe Arg Arg Leu Asp Leu Pro
140 145 150
Ser Asn Leu Pro Gly Leu Ile Leu Thr Ser Glu His Cys Asn Glu
155 160 165
Gly Val Gln Leu Pro Leu Ser Ser Leu Ser Gln Asp Ser Lys Leu
170 175 180
Val Tyr Ile Arg Leu Leu Trp Asp Asn Ile Asn Leu His Gln Glu
185 190 195
Pro Arg Glu Pro Leu Tyr Val Ser Trp Arg Asn Phe Asn Ser Glu
200 205 210
Lys Lys Ser Ser Leu Leu Ser Glu Glu Gln Gln Glu Thr Ser Thr
215 220 225
Leu Val Glu Thr Ile Arg Gln Ser Ile Gln His Asn Asn Val Leu
230 235 240

Lys Pro Ile Asn Leu Leu Ser Gln Gln Met Lys Pro Gly Met Lys
245 250 255
Arg Gln Arg Ser Leu Tyr Arg Glu Ile Leu Phe Leu Ser Leu Val
260 265 270
Ser Leu Gly Arg Glu Asn Ile Asp Ile Glu Ala Phe Asp Asn Glu
275 280 285
Tyr Gly Ile Ala Tyr Asn Ser Leu Ser Ser Glu Ile Leu Glu Arg
290 295 300
Leu Gln Lys Ile Asp Ala Pro Pro Ser Ala Ser Val Glu Trp Cys
305 310 315
Arg Lys Cys Phe Gly Ala Pro Leu Ile
320

<210> 41
<211> 270
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2775157CD1

<400> 41
Met Pro Cys Pro Met Leu Leu Pro Ser Gly Lys Val Ile Asp Gln
1 5 10 15
Ser Thr Leu Glu Lys Cys Asn Arg Ser Glu Ala Thr Trp Gly Arg
20 25 30
Val Pro Ser Asp Pro Phe Thr Gly Val Ala Phe Thr Pro His Ser
35 40 45
Gln Pro Leu Pro His Pro Ser Leu Lys Ala Arg Ile Asp His Phe
50 55 60
Leu Leu Gln His Ser Ile Pro Gly Cys His Leu Leu Gly Arg Ala
65 70 75
Gln Thr Ala Leu Ala Val Ile Pro Ser Ser Ile Val Leu Pro Ser
80 85 90
Gln Lys Arg Lys Ile Glu Gln Ala Glu His Val Pro Asp Ser Asn
95 100 105
Phe Gly Val Asn Ala Ser Cys Phe Ser Ala Thr Ser Pro Leu Val
110 115 120
Leu Pro Thr Thr Ser Glu His Thr Ala Lys Lys Met Lys Ala Thr
125 130 135
Asn Glu Pro Ser Leu Thr His Met Asp Cys Ser Thr Gly Pro Leu
140 145 150
Ser His Glu Gln Lys Leu Ser Gln Ser Leu Glu Ile Ala Leu Ala
155 160 165
Ser Thr Leu Gly Ser Met Pro Ser Phe Thr Ala Arg Leu Thr Arg
170 175 180
Gly Gln Leu Gln His Leu Gly Thr Arg Gly Ser Asn Thr Ser Trp
185 190 195
Arg Pro Gly Thr Gly Ser Glu Gln Pro Gly Ser Ile Leu Gly Pro
200 205 210
Glu Cys Ala Ser Cys Lys Arg Val Phe Ser Pro Tyr Phe Lys Lys
215 220 225
Glu Pro Val Tyr Gln Leu Pro Cys Gly His Leu Leu Cys Arg Pro
230 235 240
Cys Leu Gly Glu Lys Gln Arg Ser Leu Pro Met Thr Cys Thr Ala
245 250 255
Cys Gln Arg Pro Val Ala Ser Gln Asp Val Leu Arg Val His Phe
260 265 270

<210> 42
<211> 252

<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2918375CD1

<400> 42

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Met Leu Arg Lys Gly Ile Cys Glu Tyr His Glu Lys Asn Tyr Ala
 1               5                  10                  15
Ala Ala Leu Glu Thr Phe Thr Glu Gly Gln Lys Leu Asp Ser Ala
                20                  25                  30
Asp Ala Asn Phe Ser Val Trp Ile Lys Arg Cys Gln Glu Ala Gln
                35                  40                  45
Asn Gly Ser Glu Ser Glu Val Trp Thr His Gln Ser Lys Ile Lys
                50                  55                  60
Tyr Asp Trp Tyr Gln Thr Glu Ser Gln Val Val Ile Thr Leu Met
                65                  70                  75
Ile Lys Asn Val Gln Lys Asn Asp Val Asn Val Glu Phe Ser Glu
                80                  85                  90
Lys Glu Leu Ser Ala Leu Val Lys Leu Pro Ser Gly Glu Asp Tyr
                95                 100                 105
Asn Leu Lys Leu Glu Leu Leu His Pro Ile Ile Pro Glu Gln Ser
               110                 115                 120
Thr Phe Lys Val Leu Ser Thr Lys Ile Glu Ile Lys Leu Lys Lys
               125                 130                 135
Pro Glu Ala Val Arg Trp Glu Lys Leu Glu Gly Gln Gly Asp Val
               140                 145                 150
Pro Thr Pro Lys Gln Phe Val Ala Asp Val Lys Asn Leu Tyr Pro
               155                 160                 165
Ser Ser Ser Pro Tyr Thr Arg Asn Trp Asp Lys Leu Val Gly Glu
               170                 175                 180
Ile Lys Glu Glu Glu Lys Asn Glu Lys Leu Glu Gly Asp Ala Ala
               185                 190                 195
Leu Asn Arg Leu Phe Gln Gln Ile Tyr Ser Asp Gly Ser Asp Glu
               200                 205                 210
Val Lys Arg Ala Met Asn Lys Ser Phe Met Glu Ser Gly Gly Thr
               215                 220                 225
Val Leu Ser Thr Asn Trp Ser Asp Val Gly Lys Arg Lys Val Glu
               230                 235                 240
Ile Asn Pro Pro Asp Asp Met Glu Trp Lys Lys Tyr
               245                 250
```

<210> 43
<211> 228
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 3149729CD1

<400> 43

```
Met Thr Met Gly Asp Lys Lys Ser Pro Thr Arg Pro Lys Arg Gln
 1               5                  10                  15
Ala Lys Pro Ala Ala Asp Glu Gly Phe Trp Asp Cys Ser Val Cys
                20                  25                  30
Thr Phe Arg Asn Ser Ala Glu Ala Phe Lys Cys Ser Ile Cys Asp
                35                  40                  45
Val Arg Lys Gly Thr Ser Thr Arg Lys Pro Arg Ile Asn Ser Gln
                50                  55                  60
```

```
Leu Val Ala Gln Gln Val Ala Gln Gln Tyr Ala Thr Pro Pro Pro
                65                  70                  75
Pro Lys Lys Glu Lys Lys Glu Lys Val Glu Lys Gln Asp Lys Glu
                80                  85                  90
Lys Pro Glu Lys Asp Lys Glu Ile Ser Pro Ser Val Thr Lys Lys
                95                  100                 105
Asn Thr Asn Lys Lys Thr Lys Pro Lys Ser Asp Ile Leu Lys Asp
                110                 115                 120
Pro Pro Ser Glu Ala Asn Ser Ile Gln Ser Ala Asn Ala Thr Thr
                125                 130                 135
Lys Thr Ser Glu Thr Asn His Thr Ser Arg Pro Arg Leu Lys Asn
                140                 145                 150
Val Asp Arg Ser Thr Ala Gln Gln Leu Ala Val Thr Val Gly Asn
                155                 160                 165
Val Thr Val Ile Ile Thr Asp Phe Lys Glu Lys Thr Arg Ser Ser
                170                 175                 180
Ser Thr Ser Ser Ser Thr Val Thr Ser Ser Ala Gly Ser Glu Gln
                185                 190                 195
Gln Asn Gln Ser Ser Ser Gly Ser Glu Ser Thr Asp Lys Gly Ser
                200                 205                 210
Ser Arg Ser Ser Thr Pro Lys Gly Asp Met Ser Ala Val Asn Asp
                215                 220                 225
Glu Ser Phe
```

<210> 44
<211> 117
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 3705895CD1

<400> 44

```
Met Ala Ala Ala Ala Ala Ala Gly Ser Gly Thr Pro Arg Glu Glu
 1               5                  10                  15
Glu Gly Pro Ala Gly Glu Ala Ala Ala Ser Gln Pro Gln Ala Pro
                20                  25                  30
Thr Ser Val Pro Gly Ala Arg Leu Ser Arg Leu Pro Leu Ala Arg
                35                  40                  45
Val Lys Ala Leu Val Lys Ala Asp Pro Asp Val Thr Leu Ala Gly
                50                  55                  60
Gln Glu Ala Ile Phe Ile Leu Ala Arg Ala Ala Glu Leu Phe Val
                65                  70                  75
Glu Thr Ile Ala Lys Asp Ala Tyr Cys Cys Ala Gln Gln Gly Lys
                80                  85                  90
Arg Lys Thr Leu Gln Arg Arg Asp Leu Asp Asn Ala Ile Glu Ala
                95                  100                 105
Val Asp Glu Phe Ala Phe Leu Glu Gly Thr Leu Asp
                110                 115
```

<210> 45
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 003256CD1

<400> 45
Met Thr Pro Lys Leu Gly Arg Gly Val Leu Glu Gly Asp Asp Val
1 5 10 15
Leu Phe Tyr Asp Glu Ser Pro Pro Pro Arg Pro Lys Leu Ser Ala
20 25 30
Leu Ala Glu Ala Lys Lys Leu Ala Ala Ile Thr Lys Leu Arg Ala
35 40 45
Lys Gly Gln Val Leu Thr Lys Thr Asn Pro Asn Ser Ile Lys Lys
50 55 60
Lys Gln Lys Asp Pro Gln Asp Ile Leu Glu Val Lys Glu Arg Val
65 70 75
Glu Lys Asn Thr Met Phe Ser Ser Gln Ala Glu Asp Glu Leu Glu
80 85 90
Pro Ala Arg Lys Lys Arg Arg Glu Gln Leu Ala Tyr Leu Glu Ser
95 100 105
Glu Glu Phe Gln Lys Ile Leu Lys Ala Lys Ser Lys His Thr Gly
110 115 120
Ile Leu Lys Glu Ala Glu Ala Glu Met Gln Glu Arg Tyr Phe Glu
125 130 135
Pro Leu Val Lys Lys Glu Gln Met Glu Glu Lys Met Arg Asn Ile
140 145 150
Arg Glu Val Lys Cys Arg Val Val Thr Cys Lys Thr Cys Ala Tyr
155 160 165
Thr His Phe Lys Leu Leu Glu Thr Cys Val Ser Glu Gln His Glu
170 175 180
Tyr His Trp His Asp Gly Val Lys Arg Phe Phe Lys Cys Pro Cys
185 190 195
Gly Asn Arg Ser Ile Ser Leu Asp Arg Leu Pro Asn Lys His Cys
200 205 210
Ser Asn Cys Gly Leu Tyr Lys Trp Glu Arg Asp Gly Met Leu Lys
215 220 225
Glu Lys Thr Gly Pro Lys Ile Gly Gly Glu Thr Leu Leu Pro Arg
230 235 240
Gly Glu Glu His Ala Lys Phe Leu Asn Ser Leu Lys
245 250

<210> 46
<211> 530
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 156986CD1

<400> 46
Met Ala Lys Gly Glu Gly Ala Glu Ser Gly Ser Ala Ala Gly Leu
1 5 10 15
Leu Pro Thr Ser Ile Leu Gln Ser Thr Glu Arg Pro Ala Gln Val
20 25 30
Lys Lys Glu Pro Lys Lys Lys Lys Gln Gln Leu Ser Val Cys Asn
35 40 45
Lys Leu Cys Tyr Ala Leu Gly Gly Ala Pro Tyr Gln Val Thr Gly
50 55 60
Cys Ala Leu Gly Phe Phe Leu Gln Ile Tyr Leu Leu Asp Val Ala
65 70 75
Gln Val Gly Pro Phe Ser Ala Ser Ile Ile Leu Phe Val Gly Arg
80 85 90
Ala Trp Asp Ala Ile Thr Asp Pro Leu Val Gly Leu Cys Ile Ser
95 100 105
Lys Ser Pro Trp Thr Cys Leu Gly Arg Leu Met Pro Trp Ile Ile
110 115 120

```
Phe Ser Thr Pro Leu Ala Val Ile Ala Tyr Phe Leu Ile Trp Phe
                125                 130                 135
Val Pro Asp Phe Pro His Gly Gln Thr Tyr Trp Tyr Leu Leu Phe
                140                 145                 150
Tyr Cys Leu Phe Glu Thr Met Val Thr Cys Phe His Val Pro Tyr
                155                 160                 165
Ser Ala Leu Thr Met Phe Ile Ser Thr Glu Gln Thr Glu Arg Asp
                170                 175                 180
Ser Ala Thr Ala Tyr Arg Met Thr Val Glu Val Leu Gly Thr Val
                185                 190                 195
Leu Gly Thr Ala Ile Gln Gly Gln Ile Val Gly Gln Ala Asp Thr
                200                 205                 210
Pro Cys Phe Gln Asp Leu Asn Ser Ser Thr Val Ala Ser Gln Ser
                215                 220                 225
Ala Asn His Thr His Gly Thr Thr Ser His Arg Glu Thr Gln Lys
                230                 235                 240
Ala Tyr Leu Leu Ala Ala Gly Val Ile Val Cys Ile Tyr Ile Ile
                245                 250                 255
Cys Ala Val Ile Leu Ile Leu Gly Val Arg Glu Gln Arg Glu Pro
                260                 265                 270
Tyr Glu Ala Gln Gln Ser Glu Pro Ile Ala Tyr Phe Arg Gly Leu
                275                 280                 285
Arg Leu Val Met Ser His Gly Pro Tyr Ile Lys Leu Ile Thr Gly
                290                 295                 300
Phe Leu Phe Thr Ser Leu Ala Phe Met Leu Val Glu Gly Asn Phe
                305                 310                 315
Val Leu Phe Cys Thr Tyr Thr Leu Gly Phe Arg Asn Glu Phe Gln
                320                 325                 330
Asn Leu Leu Leu Ala Ile Met Leu Ser Ala Thr Leu Thr Ile Pro
                335                 340                 345
Ile Trp Gln Trp Phe Leu Thr Arg Phe Gly Lys Lys Thr Ala Val
                350                 355                 360
Tyr Val Gly Ile Ser Ser Ala Val Pro Phe Leu Ile Leu Val Ala
                365                 370                 375
Leu Met Glu Ser Asn Leu Ile Ile Thr Tyr Ala Val Ala Val Ala
                380                 385                 390
Ala Gly Ile Ser Val Ala Ala Ala Phe Leu Leu Pro Trp Ser Met
                395                 400                 405
Leu Pro Asp Val Ile Asp Asp Phe His Leu Lys Gln Pro His Phe
                410                 415                 420
His Gly Thr Glu Pro Ile Phe Phe Ser Phe Tyr Val Phe Phe Thr
                425                 430                 435
Lys Phe Ala Ser Gly Val Ser Leu Gly Ile Ser Thr Leu Ser Leu
                440                 445                 450
Asp Phe Ala Gly Tyr Gln Thr Arg Gly Cys Ser Gln Pro Glu Arg
                455                 460                 465
Val Lys Phe Thr Leu Asn Met Leu Val Thr Met Ala Pro Ile Val
                470                 475                 480
Leu Ile Leu Leu Gly Leu Leu Leu Phe Lys Met Tyr Pro Ile Asp
                485                 490                 495
Glu Glu Arg Arg Arg Gln Asn Lys Lys Ala Leu Gln Ala Leu Arg
                500                 505                 510

Asp Glu Ala Ser Ser Ser Gly Cys Ser Glu Thr Asp Ser Thr Glu
                515                 520                 525
Leu Ala Ser Ile Leu
                530
```

<210> 47
<211> 355
<212> PRT
<213> Homo sapiens

```
<220>
<221> misc_feature
<223> Incyte clone 319415CD1

<400> 47
Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Cys Ile Phe Lys
 1               5                  10                  15
Ile Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr
                20                  25                  30
Val Leu Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe
                35                  40                  45
Gln Asn Arg Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly
                50                  55                  60
Ser Leu Leu Leu Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr
                65                  70                  75
Ile Cys Glu Ile Arg Leu Lys Gly Glu Ser Gln Val Phe Lys Lys
                80                  85                  90
Ala Val Val Leu His Val Leu Pro Glu Glu Pro Lys Glu Leu Met
                95                 100                 105
Val His Val Gly Gly Leu Ile Gln Met Gly Cys Val Phe Gln Ser
               110                 115                 120
Thr Glu Val Lys His Val Thr Lys Val Glu Trp Ile Phe Ser Gly
               125                 130                 135
Arg Arg Ala Lys Glu Glu Ile Val Phe Arg Tyr Tyr His Lys Leu
               140                 145                 150
Arg Met Ser Val Glu Tyr Ser Gln Ser Trp Gly His Phe Gln Asn
               155                 160                 165
Arg Val Asn Leu Val Gly Asp Ile Phe Arg Asn Asp Gly Ser Ile
               170                 175                 180
Met Leu Gln Gly Val Arg Glu Ser Asp Gly Gly Asn Tyr Thr Cys
               185                 190                 195
Ser Ile His Leu Gly Asn Leu Val Phe Lys Lys Thr Ile Val Leu
               200                 205                 210
His Val Ser Pro Glu Glu Pro Arg Thr Leu Val Thr Pro Ala Ala
               215                 220                 225
Leu Arg Pro Leu Val Leu Gly Gly Asn Gln Leu Val Ile Ile Val
               230                 235                 240
Gly Ile Val Cys Ala Thr Ile Leu Leu Leu Pro Val Leu Ile Leu
               245                 250                 255
Ile Val Lys Lys Thr Cys Gly Asn Lys Ser Ser Val Asn Ser Thr
               260                 265                 270
Val Leu Val Lys Asn Thr Lys Lys Thr Asn Pro Glu Ile Lys Glu
               275                 280                 285
Lys Pro Cys His Phe Glu Arg Cys Glu Gly Glu Lys His Ile Tyr
               290                 295                 300
Ser Pro Ile Ile Val Arg Glu Val Ile Glu Glu Glu Glu Pro Ser
               305                 310                 315
Glu Lys Ser Glu Ala Thr Tyr Met Thr Met His Pro Val Trp Pro
               320                 325                 330
Ser Leu Arg Ser Asp Arg Asn Asn Ser Leu Glu Lys Lys Ser Gly
               335                 340                 345
Gly Gly Met Pro Lys Thr Gln Gln Ala Phe
               350                 355


<210> 48
<211> 136
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
```

<223> Incyte clone 635581CD1

<400> 48
Met Val Gly Gln Thr Glu Asp Asp Thr Ala Gln Gln Leu Val Pro
1 5 10 15
Thr Cys Gly Met Lys Gly Val Gly Glu Arg Ile Val Glu Tyr Val
20 25 30
Ser Asn Ile Pro Ala Leu Gln Arg Ala Thr Pro Lys Gly Leu Ala
35 40 45
Ser Val Ser Pro Asp Leu Glu His Arg Gln Glu Trp Thr Tyr Ser
50 55 60
Lys Ser Pro Leu Met Gly Lys Gly Thr Arg Leu Glu Ala Ser Glu
65 70 75
Asn Lys Arg Ala Gly Trp Leu Ala Ala Ala Pro Glu Asn Leu Lys
80 85 90
Tyr His Arg Gln Ile Ala Gln Gly Ala Lys Asp Tyr Glu Ile Leu
95 100 105
Lys Lys Glu Thr Asn Lys Phe Ile Leu Arg Ile Tyr Thr His Trp
110 115 120
Ser Arg Arg Ser Ile Leu Arg Lys Gly Ser Lys Gly Met Gln Asn
125 130 135
Leu

<210> 49
<211> 230
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 921803CD1

<400> 49
Met Lys Leu Ile Val Gly Ile Gly Gly Met Thr Asn Gly Gly Lys
1 5 10 15
Thr Thr Leu Thr Asn Ser Leu Leu Arg Ala Leu Pro Asn Cys Cys
20 25 30
Val Ile His Gln Asp Asp Phe Phe Lys Pro Gln Asp Gln Ile Ala
35 40 45
Val Gly Glu Asp Gly Phe Lys Gln Trp Asp Val Leu Glu Ser Leu
50 55 60
Asp Met Glu Ala Met Leu Asp Thr Val Gln Ala Trp Leu Ser Ser
65 70 75
Pro Gln Lys Phe Ala Arg Ala His Gly Val Ser Val Gln Pro Glu
80 85 90
Ala Ser Asp Thr His Ile Leu Leu Leu Glu Gly Phe Leu Leu Tyr
95 100 105
Ser Tyr Lys Pro Leu Val Asp Leu Tyr Ser Arg Arg Tyr Phe Leu
110 115 120
Thr Val Pro Tyr Glu Glu Cys Lys Trp Arg Arg Ser Thr Arg Asn
125 130 135
Tyr Thr Val Pro Asp Pro Pro Gly Leu Phe Asp Gly His Val Trp
140 145 150
Pro Met Tyr Gln Lys Tyr Arg Gln Glu Met Glu Ala Asn Gly Val
155 160 165
Glu Val Val Tyr Leu Asp Gly Met Lys Ser Arg Glu Glu Leu Phe
170 175 180
Arg Glu Val Leu Glu Asp Ile Gln Asn Ser Leu Leu Asn Arg Ser
185 190 195
Gln Glu Ser Ala Pro Ser Pro Ala Arg Pro Ala Arg Thr Gln Gly
200 205 210

Pro Gly Arg Gly Cys Gly His Arg Thr Ala Arg Pro Ala Ala Ser
215 220 225
Gln Gln Asp Ser Met
230

<210> 50
<211> 70
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1250492CD1

<400> 50
Met Thr Ile Lys Leu Arg Pro Leu Pro Phe Phe Lys Pro Lys Ser
1 5 10 15
Gly Asn Gln Glu Gln Gln Leu His Gly Leu Leu Ala Pro Asp Gln
20 25 30
Pro Gly Ser Gly Asp Ile Val Ser Leu Phe Gly Asn Cys Arg Pro
35 40 45
Gln Gly Val Gly Leu Ser His Phe Leu Val Leu Pro Thr Phe Pro
50 55 60
Ile Arg Ala Ser Ser Arg Gly Gln Val Cys
65 70

<210> 51
<211> 169
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1427838CD1

<400> 51
Met Leu Ala Phe Ser Glu Met Pro Lys Pro Pro Asp Tyr Ser Glu
1 5 10 15
Leu Ser Asp Ser Leu Thr Leu Ala Val Gly Thr Gly Arg Phe Ser
20 25 30
Gly Pro Leu His Arg Ala Trp Arg Met Met Asn Phe Arg Gln Arg
35 40 45
Met Gly Trp Ile Gly Val Gly Leu Tyr Leu Leu Ala Ser Ala Ala
50 55 60
Ala Phe Tyr Tyr Val Phe Glu Ile Ser Glu Thr Tyr Asn Arg Leu
65 70 75
Ala Leu Glu His Ile Gln Gln His Pro Glu Glu Pro Leu Glu Gly
80 85 90
Thr Thr Trp Thr His Ser Leu Lys Ala Gln Leu Leu Ser Leu Pro
95 100 105
Phe Trp Val Trp Thr Val Ile Phe Leu Val Pro Tyr Leu Gln Met
110 115 120
Phe Leu Phe Leu Tyr Ser Cys Thr Arg Ala Asp Pro Lys Thr Val
125 130 135
Gly Tyr Cys Ile Ile Pro Ile Cys Leu Ala Val Ile Cys Asn Arg
140 145 150
His Gln Ala Phe Val Lys Ala Ser Asn Gln Ile Ser Arg Leu Gln
155 160 165
Leu Ile Asp Thr

<210> 52
<211> 359
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1448258CD1

<400> 52
```
Met Gly Pro Thr Lys Phe Thr Gln Thr Asn Ile Gly Ile Ile Glu
 1               5                  10                  15
Asn Lys Leu Leu Glu Ala Pro Asp Val Leu Cys Leu Arg Leu Ser
                20                  25                  30
Thr Glu Gln Cys Gln Ala His Glu Glu Lys Gly Ile Glu Glu Leu
                35                  40                  45
Ser Asp Pro Ser Gly Pro Lys Ser Tyr Ser Ile Thr Glu Lys His
                50                  55                  60
Tyr Ala Gln Glu Asp Pro Arg Met Leu Phe Val Ala Ala Val Asp
                65                  70                  75
His Ser Ser Ser Gly Asp Met Ser Leu Leu Pro Ser Ser Asp Pro
                80                  85                  90
Lys Phe Gln Gly Leu Gly Val Val Glu Ser Ala Val Thr Ala Asn
                95                  100                 105
Asn Thr Glu Glu Ser Leu Phe Arg Ile Cys Ser Pro Leu Ser Gly
                110                 115                 120
Ala Asn Glu Tyr Ile Ala Ser Thr Asp Thr Leu Lys Thr Glu Glu
                125                 130                 135
Val Leu Leu Phe Thr Asp Gln Thr Asp Asp Leu Ala Lys Glu Glu
                140                 145                 150
Pro Thr Ser Leu Phe Gln Arg Asp Ser Glu Thr Lys Gly Glu Ser
                155                 160                 165
Gly Leu Val Leu Glu Gly Asp Lys Glu Ile His Gln Ile Phe Glu
                170                 175                 180
Asp Leu Asp Lys Lys Leu Ala Leu Ala Ser Arg Phe Tyr Ile Pro
                185                 190                 195
Glu Gly Cys Ile Gln Arg Trp Ala Ala Glu Met Val Val Ala Leu
                200                 205                 210
Asp Ala Leu His Arg Glu Gly Ile Val Cys Arg Asp Leu Asn Pro
                215                 220                 225
Asn Asn Ile Leu Leu Asn Asp Arg Gly His Ile Gln Leu Thr Tyr
                230                 235                 240
Phe Ser Arg Trp Ser Glu Val Glu Asp Ser Cys Asp Ser Asp Ala
                245                 250                 255
Ile Glu Arg Met Tyr Cys Ala Pro Glu Val Gly Ala Ile Thr Glu
                260                 265                 270
Glu Thr Glu Ala Cys Asp Trp Trp Ser Leu Gly Ala Val Leu Phe
                275                 280                 285
Glu Leu Leu Thr Gly Lys Thr Leu Val Glu Cys His Pro Ala Gly
                290                 295                 300
Ile Asn Thr His Thr Thr Leu Asn Met Pro Glu Cys Val Ser Glu
                305                 310                 315
Glu Ala Arg Ser Leu Ile Gln Gln Leu Leu Gln Phe Asn Pro Leu
                320                 325                 330
Glu Arg Leu Gly Ala Gly Val Ala Gly Val Glu Asp Ile Lys Ser
                335                 340                 345
His Pro Phe Phe Thr Pro Val Asp Trp Ala Glu Leu Met Arg
                350                 355
```

<210> 53
<211> 545

<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1645941CD1

<400> 53

```
Met Ser Arg Lys Gln Asn Gln Lys Asp Ser Ser Gly Phe Ile Phe
  1               5                  10                  15
Asp Leu Gln Ser Asn Thr Val Leu Ala Gln Gly Gly Ala Phe Glu
                 20                  25                  30
Asn Met Lys Glu Lys Ile Asn Ala Val Arg Ala Ile Val Pro Asn
                 35                  40                  45
Lys Ser Asn Asn Glu Ile Ile Leu Val Leu Gln His Phe Asp Asn
                 50                  55                  60
Cys Val Asp Lys Thr Val Gln Ala Phe Met Glu Gly Ser Ala Ser
                 65                  70                  75
Glu Val Leu Lys Glu Trp Thr Val Thr Gly Lys Lys Lys Asn Lys
                 80                  85                  90
Lys Lys Lys Asn Lys Pro Lys Pro Ala Ala Glu Pro Ser Asn Gly
                 95                 100                 105
Ile Pro Asp Ser Ser Lys Ser Val Ser Ile Gln Glu Glu Gln Ser
                110                 115                 120
Ala Pro Ser Ser Glu Lys Gly Gly Met Asn Gly Tyr His Val Asn
                125                 130                 135
Gly Ala Ile Asn Asp Thr Glu Ser Val Asp Ser Leu Ser Glu Gly
                140                 145                 150
Leu Glu Thr Leu Ser Ile Asp Ala Arg Glu Leu Glu Asp Pro Glu
                155                 160                 165
Ser Ala Met Leu Asp Thr Leu Asp Arg Thr Gly Ser Met Leu Gln
                170                 175                 180
Asn Gly Val Ser Asp Phe Glu Thr Lys Ser Leu Thr Met His Ser
                185                 190                 195
Ile His Asn Ser Gln Gln Pro Arg Asn Ala Ala Lys Ser Leu Ser
                200                 205                 210
Arg Pro Thr Thr Glu Thr Gln Phe Ser Asn Met Gly Met Glu Asp
                215                 220                 225
Val Pro Leu Ala Thr Ser Lys Lys Leu Ser Ser Asn Ile Glu Lys
                230                 235                 240
Ser Val Lys Asp Leu Gln Arg Cys Thr Val Ser Leu Ala Arg Tyr
                245                 250                 255
Arg Val Val Val Lys Glu Glu Met Asp Ala Ser Ile Lys Lys Met
                260                 265                 270
Lys Gln Ala Phe Ala Glu Leu Glu Ser Cys Leu Met Asp Arg Glu
                275                 280                 285
Val Ala Leu Leu Ala Glu Met Asp Lys Val Lys Ala Glu Ala Met
                290                 295                 300
Glu Ile Leu Leu Ser Arg Gln Lys Lys Ala Glu Leu Leu Lys Lys
                305                 310                 315
Met Thr His Val Ala Val Gln Met Ser Glu Gln Gln Leu Val Glu
                320                 325                 330
Leu Arg Ala Asp Ile Lys His Phe Val Ser Glu Arg Lys Tyr Asp
                335                 340                 345
Glu Asp Leu Gly Arg Val Ala Arg Phe Thr Cys Asp Val Glu Thr
                350                 355                 360
Leu Lys Lys Ser Ile Asp Ser Phe Gly Gln Val Ser His Pro Lys
                365                 370                 375
Asn Ser Tyr Ser Thr Arg Ser Arg Cys Ser Ser Val Thr Ser Val
                380                 385                 390
Ser Leu Ser Ser Pro Ser Asp Ala Ser Ala Ala Ser Ser Ser Thr
                395                 400                 405
Cys Ala Ser Pro Pro Ser Leu Thr Ser Ala Asn Lys Lys Asn Phe
                410                 415                 420
```

Ala Pro Gly Glu Thr Pro Ala Ala Ile Ala Asn Ser Ser Gly Gln
425 430 435
Pro Tyr Gln Pro Leu Arg Glu Val Leu Pro Gly Asn Arg Arg Gly
440 445 450
Gly Gln Gly Tyr Arg Pro Gln Gly Gln Lys Ser Asn Asp Pro Met
455 460 465
Asn Gln Gly Arg His Asp Ser Met Gly Arg Tyr Arg Asn Ser Ser
470 475 480
Trp Tyr Ser Ser Gly Ser Arg Tyr Gln Ser Ala Pro Ser Gln Ala
485 490 495
Pro Gly Asn Thr Ile Glu Arg Gly Gln Thr His Ser Ala Gly Thr
500 505 510
Asn Gly Thr Gly Val Ser Met Glu Pro Ser Pro Pro Thr Pro Ser
515 520 525
Phe Lys Lys Gly Leu Pro Gln Arg Lys Pro Arg Thr Ser Gln Thr
530 535 540
Glu Ala Val Asn Ser
545

<210> 54
<211> 99
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1646005CD1

<400> 54
Met Asn Trp Val Ala Val Leu Cys Pro Leu Gly Ile Val Trp Met
1 5 10 15
Val Gly Asp Gln Pro Pro Gln Val Leu Ser Gln Ala Ser Ser Leu
20 25 30
Ala Val Tyr Leu Arg Ala Ala Pro Tyr Pro Asp Val Thr Ala Lys
35 40 45
Lys Leu Arg His Asp Thr Asn Cys Gly Phe Pro Arg Gln Gln Arg
50 55 60
Met Ala Arg Gly His Glu Gly Arg Ala Pro Leu Leu Asp Arg Pro
65 70 75
Thr Leu Lys Ser Arg Tyr Leu Arg Ala Asn His Lys Ile Asn Thr
80 85 90
Phe Glu Glu Ile Thr Ala Met Pro Ser
95

<210> 55
<211> 565
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1686561CD1

<400> 55
Met Asn Arg Ser Ile Pro Val Glu Val Asp Glu Ser Glu Pro Tyr
1 5 10 15
Pro Ser Gln Leu Leu Lys Pro Ile Pro Glu Tyr Ser Pro Glu Glu
20 25 30
Glu Ser Glu Pro Pro Ala Pro Asn Ile Arg Asn Met Ala Pro Asn
35 40 45
Ser Leu Ser Ala Pro Thr Met Leu His Asn Ser Ser Gly Asp Phe
50 55 60

Ser Gln Ala His Ser Thr Leu Lys Leu Ala Asn His Gln Arg Pro
65 70 75
Val Ser Arg Gln Val Thr Cys Leu Arg Thr Gln Val Leu Glu Asp
80 85 90
Ser Glu Asp Ser Phe Cys Arg Arg His Pro Gly Leu Gly Lys Ala
95 100 105
Phe Pro Ser Gly Cys Ser Ala Val Ser Glu Pro Ala Ser Glu Ser
110 115 120
Val Val Gly Ala Leu Pro Ala Glu His Gln Phe Ser Phe Met Glu
125 130 135
Lys Arg Asn Gln Trp Leu Val Ser Gln Leu Ser Ala Ala Ser Pro
140 145 150
Asp Thr Gly His Asp Ser Asp Lys Ser Asp Gln Ser Leu Pro Asn
155 160 165
Ala Ser Ala Asp Ser Leu Gly Gly Ser Gln Glu Met Val Gln Arg
170 175 180
Pro Gln Pro His Arg Asn Arg Ala Gly Leu Asp Leu Pro Thr Ile
185 190 195
Asp Thr Gly Tyr Asp Ser Gln Pro Gln Asp Val Leu Gly Ile Arg
200 205 210
Gln Leu Glu Arg Pro Leu Pro Leu Thr Ser Val Cys Tyr Pro Gln
215 220 225
Asp Leu Pro Arg Pro Leu Arg Ser Arg Glu Phe Pro Gln Phe Glu
230 235 240
Pro Gln Arg Tyr Pro Ala Cys Ala Gln Met Leu Pro Pro Asn Leu
245 250 255
Ser Pro His Ala Pro Trp Asn Tyr His Tyr His Cys Pro Gly Ser
260 265 270
Pro Asp His Gln Val Pro Tyr Gly His Asp Tyr Pro Arg Ala Ala
275 280 285
Tyr Gln Gln Val Ile Gln Pro Ala Leu Pro Gly Gln Pro Leu Pro
290 295 300
Gly Ala Ser Val Arg Gly Leu His Pro Val Gln Lys Val Ile Leu
305 310 315
Asn Tyr Pro Ser Pro Trp Asp Gln Glu Glu Arg Pro Ala Gln Arg
320 325 330
Asp Cys Ser Phe Pro Gly Leu Pro Arg His Gln Asp Gln Pro His
335 340 345
His Gln Pro Pro Asn Arg Ala Gly Ala Pro Gly Glu Ser Leu Glu
350 355 360
Cys Pro Ala Glu Leu Arg Pro Gln Val Pro Gln Pro Pro Ser Pro
365 370 375
Ala Ala Val Pro Arg Pro Pro Ser Asn Pro Pro Ala Arg Gly Thr
380 385 390
Leu Lys Thr Ser Asn Leu Pro Glu Glu Leu Arg Lys Val Phe Ile
395 400 405
Thr Tyr Ser Met Asp Thr Ala Met Glu Val Val Lys Phe Val Asn
410 415 420
Phe Leu Leu Val Asn Gly Phe Gln Thr Ala Ile Asp Ile Phe Glu
425 430 435
Asp Arg Ile Arg Gly Ile Asp Ile Ile Lys Trp Met Glu Arg Tyr
440 445 450
Leu Arg Asp Lys Thr Val Met Ile Ile Val Ala Ile Ser Pro Lys
455 460 465
Tyr Lys Gln Asp Val Glu Gly Ala Glu Ser Gln Leu Asp Glu Asp
470 475 480
Glu His Gly Leu His Thr Lys Tyr Ile His Arg Met Met Gln Ile
485 490 495
Glu Phe Ile Lys Gln Gly Ser Met Asn Phe Arg Phe Ile Pro Val
500 505 510
Leu Phe Pro Asn Ala Lys Lys Glu His Val Pro Thr Trp Leu Gln
515 520 525
Asn Thr His Val Tyr Ser Trp Pro Lys Asn Lys Lys Asn Ile Leu
530 535 540

```
Leu Arg Leu Leu Arg Glu Glu Glu Tyr Val Ala Pro Pro Arg Gly
                545                 550                 555
Pro Leu Pro Thr Leu Gln Val Val Pro Leu
                560                 565
```

<210> 56
<211> 197
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1821233CD1

<400> 56

```
Met Thr Pro Thr Ser Ser Phe Val Ser Pro Pro Pro Pro Thr Ala
  1               5                  10                  15
Ser Pro His Ser Asn Arg Thr Thr Pro Pro Glu Ala Ala Gln Asn
                 20                  25                  30
Gly Gln Ser Pro Met Ala Ala Leu Ile Leu Val Ala Asp Asn Ala
                 35                  40                  45
Gly Gly Ser His Ala Ser Lys Asp Ala Asn Gln Val His Ser Thr
                 50                  55                  60
Thr Arg Arg Asn Ser Asn Ser Pro Pro Ser Pro Ser Ser Met Asn
                 65                  70                  75
Gln Arg Arg Leu Gly Pro Arg Glu Val Gly Gly Gln Gly Ala Gly
                 80                  85                  90
Asn Thr Gly Gly Leu Glu Pro Val His Pro Ala Ser Leu Pro Asp
                 95                 100                 105
Ser Ser Leu Ala Thr Ser Ala Pro Leu Cys Cys Thr Leu Cys His
                110                 115                 120
Glu Arg Leu Glu Asp Thr His Phe Val Gln Cys Pro Ser Val Pro
                125                 130                 135
Ser His Lys Phe Cys Phe Pro Cys Ser Arg Gln Ser Ile Lys Gln
                140                 145                 150
Gln Gly Ala Ser Gly Glu Val Tyr Cys Pro Ser Gly Glu Lys Cys
                155                 160                 165
Pro Leu Val Gly Ser Asn Val Pro Trp Ala Phe Met Gln Gly Glu
                170                 175                 180
Ile Ala Thr Ile Leu Ala Gly Asp Val Lys Val Lys Lys Glu Arg
                185                 190                 195
Asp Ser
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<210> 57
<211> 321
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1877278CD1

<400> 57

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Met Lys Glu Asp Cys Leu Pro Ser Ser His Val Pro Ile Ser Asp
  1               5                  10                  15
Ser Lys Ser Ile Gln Lys Ser Glu Leu Leu Gly Leu Leu Lys Thr
                 20                  25                  30
Tyr Asn Cys Tyr His Glu Gly Lys Ser Phe Gln Leu Arg His Arg
                 35                  40                  45
```

```
Glu Glu Glu Gly Thr Leu Ile Ile Glu Gly Leu Leu Asn Ile Ala
                50                  55                  60
Trp Gly Leu Arg Arg Pro Ile Arg Leu Gln Met Gln Asp Asp Arg
                65                  70                  75
Glu Gln Val His Leu Pro Ser Thr Ser Trp Met Pro Arg Arg Pro
                80                  85                  90
Ser Cys Pro Leu Lys Glu Pro Ser Pro Gln Asn Gly Asn Ile Thr
                95                  100                 105
Ala Gln Gly Pro Ser Ile Gln Pro Val His Lys Ala Glu Ser Ser
                110                 115                 120
Thr Asp Ser Ser Gly Pro Leu Glu Glu Ala Glu Glu Ala Pro Gln
                125                 130                 135
Leu Met Arg Thr Lys Ser Asp Ala Ser Cys Met Ser Gln Arg Arg
                140                 145                 150
Pro Lys Cys Arg Ala Pro Gly Glu Ala Gln Arg Ile Arg Arg His
                155                 160                 165
Arg Phe Ser Ile Asn Gly His Phe Tyr Asn His Lys Thr Ser Val
                170                 175                 180
Phe Thr Pro Ala Tyr Gly Ser Val Thr Asn Val Arg Val Asn Ser
                185                 190                 195
Thr Met Thr Thr Leu Gln Val Leu Thr Leu Leu Leu Asn Lys Phe
                200                 205                 210
Arg Val Glu Asp Gly Pro Ser Glu Phe Ala Leu Tyr Ile Val His
                215                 220                 225
Glu Ser Gly Glu Arg Thr Lys Leu Lys Asp Cys Glu Tyr Pro Leu
                230                 235                 240
Ile Ser Arg Ile Leu His Gly Pro Cys Glu Lys Ile Ala Arg Ile
                245                 250                 255
Phe Leu Met Glu Ala Asp Leu Gly Val Glu Val Pro His Glu Val
                260                 265                 270
Ala Gln Tyr Ile Lys Phe Glu Met Pro Val Leu Asp Ser Phe Val
                275                 280                 285
Glu Lys Leu Lys Glu Glu Glu Glu Arg Glu Ile Ile Lys Leu Thr
                290                 295                 300
Met Lys Phe Gln Ala Leu Arg Leu Thr Met Leu Gln Arg Leu Glu
                305                 310                 315
Gln Leu Val Glu Ala Lys
                320
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<210> 58
<211> 356
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1880692CD1

<400> 58

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Met Glu Trp Leu Lys Ser Thr Asp Tyr Gly Lys Tyr Glu Gly Leu
 1              5                   10                  15
Thr Lys Asn Tyr Met Asp Tyr Leu Ser Arg Leu Tyr Glu Arg Glu
                20                  25                  30
Ile Lys Asp Phe Phe Glu Val Ala Lys Ile Lys Met Thr Gly Thr
                35                  40                  45
Thr Lys Glu Ser Lys Lys Phe Gly Leu His Gly Ser Ser Gly Lys
                50                  55                  60
Leu Thr Gly Ser Thr Ser Ser Leu Asn Lys Leu Ser Val Gln Ser
                65                  70                  75
Ser Gly Asn Arg Arg Ser Gln Ser Ser Ser Leu Leu Asp Met Gly
                80                  85                  90
Asn Met Ser Ala Ser Asp Leu Asp Val Ala Asp Arg Thr Lys Phe
                95                  100                 105
```

```
Asp Lys Ile Phe Glu Gln Val Leu Ser Glu Leu Glu Pro Leu Cys
                110                 115                 120
Leu Ala Glu Gln Asp Phe Ile Ser Lys Phe Phe Lys Leu Gln Gln
                125                 130                 135
His Gln Ser Met Pro Gly Thr Met Ala Glu Ala Glu Asp Leu Asp
                140                 145                 150
Gly Gly Thr Leu Ser Arg Gln His Asn Cys Gly Thr Pro Leu Pro
                155                 160                 165
Val Ser Ser Glu Lys Asp Met Ile Arg Gln Met Met Ile Lys Ile
                170                 175                 180
Phe Arg Cys Ile Glu Pro Glu Leu Asn Asn Leu Ile Ala Leu Gly
                185                 190                 195
Asp Lys Ile Asp Ser Phe Asn Ser Leu Tyr Met Leu Val Lys Met
                200                 205                 210
Ser His His Val Trp Thr Ala Gln Asn Val Asp Pro Ala Ser Phe
                215                 220                 225
Leu Ser Thr Thr Leu Gly Asn Val Leu Val Thr Val Lys Arg Asn
                230                 235                 240
Phe Asp Lys Cys Ile Ser Asn Gln Ile Arg Gln Met Glu Glu Val
                245                 250                 255
Lys Ile Ser Lys Lys Ser Lys Val Gly Ile Leu Pro Phe Val Ala
                260                 265                 270
Glu Phe Glu Glu Phe Ala Gly Leu Ala Glu Ser Ile Phe Lys Asn
                275                 280                 285
Ala Glu Arg Arg Gly Asp Leu Asp Lys Ala Tyr Thr Lys Leu Ile
                290                 295                 300
Arg Gly Val Phe Val Asn Val Glu Lys Val Ala Asn Glu Ser Gln
                305                 310                 315
Lys Thr Pro Arg Asp Val Val Met Met Glu Asn Phe His His Ile
                320                 325                 330
Phe Ala Thr Leu Ser Arg Leu Lys Ile Ser Cys Leu Glu Ala Glu
                335                 340                 345
Lys Lys Glu Ala Ala Ile Asn His Lys Phe Phe
                350                 355
```

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<210> 59
<211> 299
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2280456CD1

<400> 59
Met Glu Glu Leu Leu Pro Asp Gly Gln Ile Trp Ala Asn Met Asp
 1              5                   10                  15
Pro Glu Glu Arg Met Leu Ala Ala Ala Thr Ala Phe Thr His Ile
                20                  25                  30
Cys Ala Gly Gln Gly Glu Gly Asp Val Arg Arg Glu Ala Gln Ser
                35                  40                  45
Ile Gln Tyr Asp Pro Tyr Ser Lys Ala Ser Val Ala Pro Gly Lys
                50                  55                  60
Arg Pro Ala Leu Pro Val Gln Leu Gln Tyr Pro His Val Glu Ser
                65                  70                  75
Asn Val Pro Ser Glu Thr Val Ser Glu Ala Ser Gln Arg Leu Arg
                80                  85                  90
Lys Pro Val Met Lys Arg Lys Val Leu Arg Arg Lys Pro Asp Gly
                95                  100                 105
Glu Val Leu Val Thr Asp Glu Ser Ile Ile Ser Glu Ser Glu Ser
                110                 115                 120
Gly Thr Glu Asn Asp Gln Asp Leu Trp Asp Leu Arg Gln Arg Leu
                125                 130                 135
```

Met Asn Val Gln Phe Gln Glu Asp Lys Glu Ser Ser Phe Asp Val
140 145 150
Ser Gln Lys Phe Asn Leu Pro His Glu Tyr Gln Gly Ile Ser Gln
155 160 165
Asp Gln Leu Ile Cys Ser Leu Gln Arg Glu Gly Met Gly Ser Pro
170 175 180
Ala Tyr Glu Gln Asp Leu Ile Val Ala Ser Arg Pro Lys Ser Phe
185 190 195
Ile Leu Pro Lys Leu Asp Gln Leu Ser Arg Asn Arg Gly Lys Thr
200 205 210
Asp Arg Val Ala Arg Tyr Phe Glu Tyr Lys Arg Asp Trp Asp Ser
215 220 225
Ile Arg Leu Pro Gly Glu Asp His Arg Lys Glu Leu Arg Trp Gly
230 235 240
Val Arg Glu Gln Met Leu Cys Arg Ala Glu Pro Gln Ser Lys Pro
245 250 255
Gln His Ile Tyr Val Pro Asn Asn Tyr Leu Val Pro Thr Glu Lys
260 265 270
Lys Arg Ser Ala Leu Arg Trp Gly Val Arg Cys Asp Leu Ala Asn
275 280 285
Gly Val Ile Pro Arg Lys Leu Pro Phe Pro Leu Ser Pro Ser
290 295

<210> 60
<211> 293
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2284580CD1

<400> 60
Met Ala Thr Phe Ser Gly Pro Ala Gly Pro Ile Leu Ser Leu Asn
1 5 10 15
Pro Gln Glu Asp Val Glu Phe Gln Lys Glu Val Ala Gln Val Arg
20 25 30
Lys Arg Ile Thr Gln Arg Lys Lys Gln Glu Gln Leu Thr Pro Gly
35 40 45
Val Val Tyr Val Arg His Leu Pro Asn Leu Leu Asp Glu Thr Gln
50 55 60
Ile Phe Ser Tyr Phe Ser Gln Phe Gly Thr Val Thr Arg Phe Arg
65 70 75
Leu Ser Arg Ser Lys Arg Thr Gly Asn Ser Lys Gly Tyr Ala Phe
80 85 90
Val Glu Phe Glu Ser Glu Asp Val Ala Lys Ile Val Ala Glu Thr
95 100 105
Met Asn Asn Tyr Leu Phe Gly Glu Arg Leu Leu Glu Cys His Phe
110 115 120
Met Pro Pro Glu Lys Val His Lys Glu Leu Phe Lys Asp Trp Asn
125 130 135
Ile Pro Phe Lys Gln Pro Ser Tyr Pro Ser Val Lys Arg Tyr Asn
140 145 150
Arg Asn Arg Thr Leu Thr Gln Lys Leu Arg Met Glu Glu Arg Phe
155 160 165
Lys Lys Lys Glu Arg Leu Leu Arg Lys Lys Leu Ala Lys Lys Gly
170 175 180
Ile Asp Tyr Asp Phe Pro Ser Leu Ile Leu Gln Lys Thr Glu Ser
185 190 195
Ile Ser Lys Thr Asn Arg Gln Thr Ser Thr Lys Gly Gln Val Leu
200 205 210

Arg Lys Lys Lys Lys Lys Val Ser Gly Thr Leu Asp Thr Pro Glu
215 220 225
Lys Thr Val Asp Ser Gln Gly Pro Thr Pro Val Cys Thr Pro Thr
230 235 240
Phe Leu Glu Arg Arg Lys Ser Gln Val Ala Glu Leu Asn Asp Asp
245 250 255
Asp Lys Asp Asp Glu Ile Val Phe Lys Gln Pro Ile Ser Cys Val
260 265 270
Lys Glu Glu Ile Gln Glu Thr Gln Thr Pro Thr His Ser Arg Lys
275 280 285
Lys Arg Arg Arg Ser Ser Asn Gln
290

<210> 61
<211> 777
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2779172CD1

<400> 61
Met Val Leu Cys His Ser Phe Leu Tyr Arg Ile Leu Thr Val Gln
1 5 10 15
Gln His Gly Phe Phe Phe Gly His Asp Arg Arg Pro Ala Asp Gly
20 25 30
Glu Lys Gln Ala Ala Thr His Val Ser Leu Asp Gln Glu Tyr Asp
35 40 45
Ser Glu Ser Ser Gln Gln Trp Arg Glu Leu Glu Glu Gln Val Val
50 55 60
Ser Val Val Asn Lys Gly Val Ile Pro Ser Asn Phe His Pro Thr
65 70 75
Gln Tyr Cys Leu Asn Ser Tyr Ser Asp Asn Ser Arg Phe Pro Leu
80 85 90
Ala Val Val Glu Glu Pro Ile Thr Val Glu Val Ala Phe Arg Asn
95 100 105
Pro Leu Lys Val Leu Leu Leu Leu Thr Asp Leu Ser Leu Leu Trp
110 115 120
Lys Phe His Pro Lys Asp Phe Ser Gly Lys Asp Asn Glu Glu Val
125 130 135
Lys Gln Leu Val Thr Ser Glu Pro Glu Met Ile Gly Ala Glu Val
140 145 150
Ile Ser Glu Phe Leu Ile Asn Gly Glu Glu Ser Lys Val Ala Arg
155 160 165
Leu Lys Leu Phe Pro His His Ile Gly Glu Leu His Ile Leu Gly
170 175 180
Val Val Tyr Asn Leu Gly Thr Ile Gln Gly Ser Met Thr Val Asp
185 190 195
Gly Ile Gly Ala Leu Pro Gly Cys His Thr Gly Lys Tyr Ser Leu
200 205 210
Ser Met Ser Val Arg Gly Lys Gln Asp Leu Glu Ile Gln Gly Pro
215 220 225
Arg Leu Asn Asn Thr Lys Glu Glu Lys Thr Ser Val Lys Tyr Gly
230 235 240
Pro Asp Arg Arg Leu Asp Pro Ile Ile Thr Glu Glu Met Pro Leu
245 250 255
Leu Glu Val Phe Phe Ile His Phe Pro Thr Gly Leu Leu Cys Gly
260 265 270
Glu Ile Arg Lys Ala Tyr Val Glu Phe Val Asn Val Ser Lys Cys
275 280 285

Pro Leu Thr Gly Leu Lys Val Val Ser Lys Arg Pro Glu Phe Phe
290 295 300
Thr Phe Gly Gly Asn Thr Ala Val Leu Thr Pro Leu Ser Pro Ser
305 310 315
Ala Ser Glu Asn Cys Ser Ala Tyr Lys Thr Val Val Thr Asp Ala
320 325 330
Thr Ser Val Cys Thr Ala Leu Ile Ser Ser Ala Ser Ser Val Asp
335 340 345
Phe Gly Ile Gly Thr Gly Ser Gln Pro Glu Val Ile Pro Val Pro
350 355 360
Leu Pro Asp Thr Val Leu Leu Pro Gly Ala Ser Val Gln Leu Pro
365 370 375
Met Trp Leu Arg Gly Pro Asp Glu Glu Gly Val His Glu Ile Asn
380 385 390
Phe Leu Phe Tyr Tyr Glu Ser Val Lys Lys Gln Pro Lys Ile Arg
395 400 405
His Arg Ile Leu Arg His Thr Ala Ile Ile Cys Thr Ser Arg Ser
410 415 420
Leu Asn Val Arg Ala Thr Val Cys Arg Ser Asn Ser Leu Glu Asn
425 430 435
Glu Glu Gly Arg Gly Gly Asn Met Leu Val Phe Val Asp Val Glu
440 445 450
Asn Thr Asn Thr Ser Glu Ala Gly Val Lys Glu Phe His Ile Val
455 460 465
Gln Val Ser Ser Ser Ser Lys His Trp Lys Leu Gln Lys Ser Val
470 475 480
Asn Leu Ser Glu Asn Lys Asp Thr Lys Leu Ala Ser Arg Glu Lys
485 490 495
Gly Lys Phe Cys Phe Lys Ala Ile Arg Cys Glu Lys Glu Glu Ala
500 505 510
Ala Thr Gln Ser Ser Glu Lys Tyr Thr Phe Ala Asp Ile Ile Phe
515 520 525
Gly Asn Glu Gln Ile Ile Ser Ser Ala Ser Pro Cys Ala Asp Phe
530 535 540
Phe Tyr Arg Ser Leu Ser Ser Glu Leu Lys Lys Pro Gln Ala His
545 550 555
Leu Pro Val His Thr Glu Lys Gln Ser Thr Glu Asp Ala Val Arg
560 565 570
Leu Ile Gln Lys Cys Ser Glu Val Asp Leu Asn Ile Val Ile Leu
575 580 585
Trp Lys Ala Tyr Val Val Glu Asp Ser Lys Gln Leu Ile Leu Glu
590 595 600
Gly Gln His His Val Ile Leu Arg Thr Ile Gly Lys Glu Ala Phe
605 610 615
Ser Tyr Pro Gln Lys Gln Glu Pro Pro Glu Met Glu Leu Leu Lys
620 625 630
Phe Phe Arg Pro Glu Asn Ile Thr Val Ser Ser Arg Pro Ser Val
635 640 645
Glu Gln Leu Ser Ser Leu Ile Lys Thr Ser Leu His Tyr Pro Glu
650 655 660
Ser Phe Asn His Pro Phe His Gln Lys Ser Leu Cys Leu Val Pro
665 670 675
Val Thr Leu Leu Leu Ser Asn Cys Ser Lys Ala Asp Val Asp Val
680 685 690
Ile Val Asp Leu Arg His Lys Thr Thr Ser Pro Glu Ala Leu Glu
695 700 705
Ile His Gly Ser Phe Thr Trp Leu Gly Gln Thr Gln Tyr Lys Leu
710 715 720
Gln Leu Lys Ser Gln Glu Ile His Ser Leu Gln Leu Lys Ala Cys
725 730 735
Phe Val His Thr Gly Val Tyr Asn Leu Gly Thr Pro Arg Val Phe
740 745 750
Ala Lys Leu Ser Asp Gln Val Thr Val Phe Glu Thr Ser Gln Gln
755 760 765

Asn Ser Met Pro Ala Leu Ile Ile Ile Ser Asn Val
770 775

<210> 62
<211> 97
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 3279329CD1

<400> 62
Met Pro Pro Gly Thr Val Leu Arg Tyr Val Gln Cys Leu Phe Leu
1 5 10 15
Asp Leu Cys Ile Cys His Glu Ala Pro Cys Gly Leu Cys Met Lys
20 25 30
Leu Leu Leu Cys Phe Trp Val Asn Arg Cys Ala Cys Gln Leu Ala
35 40 45
Cys Val Leu Ser Lys Phe His Lys Leu Lys Val Phe Lys Gly Cys
50 55 60
Val Val Ser Glu Leu Tyr Val Ser Phe Leu Ser Leu Tyr Leu Gln
65 70 75
Arg Val Arg Asn Glu Ile Tyr Thr Ser Lys Val Ser Leu Ile Asn
80 85 90
Met Ala Phe Cys Phe Ser Met
95

<210> 63
<211> 308
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 3340290CD1

<400> 63
Met Ser Val Ser Gly Leu Lys Ala Glu Leu Lys Phe Leu Ala Ser
1 5 10 15
Ile Phe Asp Lys Asn His Glu Arg Phe Arg Ile Val Ser Trp Lys
20 25 30
Leu Asp Glu Leu His Cys Gln Phe Leu Val Pro Gln Gln Gly Ser
35 40 45
Pro His Ser Leu Pro Pro Pro Leu Thr Leu His Cys Asn Ile Thr
50 55 60
Glu Ser Tyr Pro Ser Ser Ser Pro Ile Trp Phe Val Asp Ser Glu
65 70 75
Asp Pro Asn Leu Thr Ser Val Leu Glu Arg Leu Glu Asp Thr Lys
80 85 90
Asn Asn Asn Leu Asn Gly Thr Thr Glu Glu Val Thr Ser Glu Glu
95 100 105
Glu Glu Glu Glu Glu Glu Met Ala Glu Asp Ile Glu Asp Leu Asp
110 115 120
His Tyr Glu Met Lys Glu Glu Glu Pro Ile Ser Gly Lys Lys Ser
125 130 135
Glu Asp Glu Gly Ile Glu Lys Glu Asn Leu Ala Ile Leu Glu Lys
140 145 150
Ile Arg Lys Thr Gln Arg Gln Asp His Leu Asn Gly Ala Val Ser
155 160 165

Gly Ser Val Gln Ala Ser Asp Arg Leu Met Lys Glu Leu Arg Asp
170 175 180
Ile Tyr Arg Ser Gln Ser Tyr Lys Thr Gly Ile Tyr Ser Val Glu
185 190 195
Leu Ile Asn Asp Ser Leu Tyr Asp Trp His Val Lys Leu Gln Lys
200 205 210
Val Asp Pro Asp Ser Pro Leu His Ser Asp Leu Gln Ile Leu Lys
215 220 225
Glu Lys Glu Gly Ile Glu Tyr Ile Leu Leu Asn Phe Ser Phe Lys
230 235 240
Asp Asn Phe Pro Phe Asp Pro Pro Phe Val Arg Val Val Leu Pro
245 250 255
Val Leu Ser Gly Gly Tyr Val Leu Gly Gly Gly Ala Leu Cys Met
260 265 270
Glu Leu Leu Thr Lys Gln Asn Gln Tyr Asn Leu Ala Arg Ala Gln
275 280 285
Gln Ser Tyr Asn Ser Ile Val Gln Ile His Glu Lys Asn Gly Trp
290 295 300
Tyr Thr Pro Pro Lys Glu Asp Gly
305

<210> 64
<211> 290
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 3376404CD1

<400> 64
Met Arg Arg Pro Ala Ala Val Pro Leu Leu Leu Leu Leu Cys Phe
1 5 10 15
Gly Ser Gln Arg Ala Lys Ala Ala Thr Ala Cys Gly Arg Pro Arg
20 25 30
Met Leu Asn Arg Met Val Gly Gly Gln Asp Thr Gln Glu Gly Glu
35 40 45
Trp Pro Trp Gln Val Ser Ile Gln Arg Asn Gly Ser His Phe Cys
50 55 60
Gly Gly Ser Leu Ile Ala Glu Gln Trp Val Leu Thr Ala Ala His
65 70 75
Cys Phe Arg Asn Thr Ser Glu Thr Ser Leu Tyr Gln Val Leu Leu
80 85 90
Gly Ala Arg Gln Leu Val Gln Pro Gly Pro His Ala Met Tyr Ala
95 100 105
Arg Val Arg Gln Val Glu Ser Asn Pro Leu Tyr Gln Gly Thr Ala
110 115 120
Ser Ser Ala Asp Val Ala Leu Val Glu Leu Glu Ala Pro Val Pro
125 130 135
Phe Thr Asn Tyr Ile Leu Pro Val Cys Leu Pro Asp Pro Ser Val
140 145 150
Ile Phe Glu Thr Gly Met Asn Cys Trp Val Thr Gly Trp Gly Ser
155 160 165
Pro Ser Glu Glu Asp Leu Leu Pro Glu Pro Arg Ile Leu Gln Lys
170 175 180
Leu Ala Val Pro Ile Ile Asp Thr Pro Lys Cys Asn Leu Leu Tyr
185 190 195
Ser Lys Asp Thr Glu Phe Gly Tyr Gln Pro Lys Thr Ile Lys Asn
200 205 210
Asp Met Leu Cys Ala Gly Phe Glu Glu Gly Lys Lys Asp Ala Cys
215 220 225
Lys Gly Asp Ser Gly Gly Pro Leu Val Cys Leu Val Gly Gln Ser
230 235 240

Trp Leu Gln Ala Gly Val Ile Ser Trp Gly Glu Gly Cys Ala Arg
245 250 255
Gln Asn Arg Pro Gly Val Tyr Ile Arg Val Thr Ala His His Asn
260 265 270
Trp Ile His Arg Ile Ile Pro Lys Leu Gln Phe Gln Pro Ala Arg
275 280 285
Leu Gly Gly Gln Lys
290

<210> 65
<211> 198
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 4173111CD1

<400> 65
Met Glu Met Ser Gly Leu Ser Phe Ser Glu Met Glu Gly Cys Arg
1 5 10 15
Asn Leu Leu Gly Leu Leu Asp Asn Asp Glu Ile Met Ala Leu Cys
20 25 30
Asp Thr Val Thr Asn Arg Leu Val Gln Pro Gln Asp Arg Gln Asp
35 40 45
Ala Val His Ala Ile Leu Ala Tyr Ser Gln Ser Ala Glu Glu Leu
50 55 60
Leu Arg Arg Arg Lys Val His Arg Glu Val Ile Phe Lys Tyr Leu
65 70 75
Ala Thr Gln Gly Ile Val Ile Pro Pro Ala Thr Glu Lys His Asn
80 85 90
Leu Ile Gln His Ala Lys Asp Tyr Trp Gln Lys Gln Pro Gln Leu
95 100 105
Lys Leu Lys Glu Thr Pro Glu Pro Val Thr Lys Thr Glu Asp Ile
110 115 120
His Leu Phe Gln Gln Gln Val Lys Glu Asp Lys Lys Ala Glu Lys
125 130 135
Val Asp Phe Arg Arg Leu Gly Glu Glu Phe Cys His Trp Phe Phe
140 145 150
Gly Leu Leu Asn Ser Gln Asn Pro Phe Leu Gly Pro Pro Gln Asp
155 160 165
Glu Trp Gly Pro Gln His Phe Trp His Asp Val Lys Leu Arg Phe
170 175 180
Tyr Tyr Asn Thr Ser Glu Gln Asn Val Met Gly Leu Thr Met Glu
185 190 195
Pro Glu Ser

<210> 66
<211> 789
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 001106CB1

<400> 66
atatatacgt atataccccct cttgcccttg aaggccggaa gtcggtctta cagataaaag 60
cgaaacagga agtcccgccc ctctatggaa agtaaatggt agctcggaag ggtcaaaaga 120
gtccgcggtt tcgccgcgtg agttgctttt tgcggctggg gaggtctacg cttctagagc 180

ttgagccagc ggggcgaccc tgcagtggca ggactcggca ccgcgccctc caccgccggt 240
tggtggcctg cgtgacagtt tcctcccgtc gacatcgaaa ggaagccgga cgtgggcggg 300
cagagagctt catcgcagta ggaatggcag ccccatctat gaaggaaaga caggtctgct 360
gggggcccg ggatgagtac tggaagtgtt tagatgagaa cttagaggat gcttctcaat 420
gcaagaagtt aagaagctct ttcgaatcaa gttgtcccca acagtggata aaatattttg 480
ataaaagaag agactactta aaattcaaag aaaaatttga agcaggacaa tttgagcctt 540
cagaaacaac tgcaaaatcc taggctgttc ataaagattg aaagtattct ttctggacat 600
tgaaaaagct ccactgacta tggaacagta atagtttgaa tcatagtgaa catcaatact 660
tgttccctat atacgacact tgataattaa gatgatcaag aaccagaaga tctgtgaaga 720
aatgaaataa aatggtattt agtaagaaat ctctatttta agaaaaaaag taaaacctgt 780
tataaacaa 789

<210> 67
<211> 1117
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 004586CB1

<400> 67
gccagagcgc ttcggccttc ccgacctctc cccggagccc cgggcctccc cggctgcttc 60
cctgagtcct tcctcctctc gccagagccc gagcgcccct cggagaccct cggctttccc 120
cgtccgctct cccggaggca gcgcggggct ataggacgaa gttatacgga agcgtctcct 180
cattgatgga gatggtgctg gagatgatcg gagaattaat ctgctagtga agagtttcat 240
taaatggtgc aactctgggt cccaggaaga gggatatagc cagtaccaac gtatgctgag 300
cacgctgtct caatgtgaat tttcaatggg caaaacttta ctagtatatg atatgaatct 360
cagagaaatg gaaaattatg aaaaaattta caaggaaata gaatgtagca tagctggagc 420
acatgaaaaa attgctgagt gcaaaaagca aattcttcaa gcaaaacgaa tacgaaaaaa 480
tcgccaagaa tatgatgctt tggcaaaagt gattcagcac catccagaca ggcatgagac 540
attaaaggaa ctagaggctc tgggaaaaga attagagcat ctttcacaca ttaaagaaag 600
tgttgaagat aagctggaat tgagacggaa acagtttcat gttcttctta gtaccatcca 660
tgaacttcag caaacattgg aaaatgatga aaaactctca gaggtagaag aagctcagga 720
agcaagcatg gaaacagatc ctaagccata gacaggctaa ttgcccacca ctcccaggaa 780
tattgaaata gctacatgac cataatgtgt ttaaaatgtg gtatgctctt gagatattta 840
aagttttggc agtaaaatac tctgttttta agtatgaatg tatttcattc atatttcctc 900
tcacaaagga aaatgacttc agtatagatt tgtttttatt aaaatgcatt ttttattctt 960
aagtggtagg aagcaacatc caaaaatgct taataaaatg cttttaagct gcaaaaaaga 1020

annnaaanga gcantnanng ntgggggcnc cnntngtaaa ananaaaggg gnggnccccc 1080
ggntannttg aancccatcn ncccccggga tttaatt 1117

<210> 68
<211> 1628
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 052927CB1

<400> 68
ggcggcggcg acgactgcag ctcgggaggt agcggcctgg cgagggacgg gccggctgcc 60
ctctcggacg gccgcggcgg agggcaaaaa tggcggaggc ttcggcggcc ggggcggact 120
cgggcgccgc tgtagccgcc caccggtttt tctgccactt ttgcaagggc gaggtcagcc 180
ccaaactacc ggaatatata tgtcccagat gtgaatcagg ctttattgaa gaagtgacag 240
atgattccag ttttttaggt ggtggcggca gtcggataga caataccaca acaacacatt 300
ttgcagagct ttggggccat ttggatcaca cgatgttttt tcaagatttt agaccctttc 360
taagtagcag tccactggac caagataata gagccaatga aaggggtcac cagactcaca 420
ctgacttctg gggagcaaga cctccacggt tgccattggg tcggagatac agatctcgag 480
gaagttctcg tcctgacaga tctccagcta ttgaaggaat actacaacac atctttgcag 540

gattttttgc aaattctgcc attcctggat ctccacaccc tttttcctgg agcgggatgc 600
tgcacttcaa ccctggggac tatgcctggg gtcagacagg gcttgatgcc attgtaaccc 660
agcttttagg acaactggaa aacacaggcc ctccccccagc tgacaaggaa aagatcacat 720
ctcttccaac agtgacagta actcaggaac aagttgatat gggtttagag tgtccagtat 780
gcaaagaaga ttacacagtt gaagaggaag tccggcagtt accttgcaat cacttctttc 840
acagcagttg tattgtgccg tggctagaac tgcatgacac atgtcctgta tgtaggaaga 900
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<213> Homo sapiens

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<223> Incyte clone 082843CB1

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<211> 1864

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<213> Homo sapiens

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<211> 2738
<212> DNA
<213> Homo sapiens

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<223> Incyte clone 397663CB1

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<213> Homo sapiens

<220>
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<223> Incyte clone 1504753CB1

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<213> Homo sapiens

<220>
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caaggttcat acgttgtcca gctgtaagtt catttgagta gcagacctaa caaatatttg 1500
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<210> 75
<211> 1624
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1805061CB1

<400> 75
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aaaa 1624

<210> 76
<211> 1675
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1850120CB1

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<210> 77
<211> 1319
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1852290CB1

<400> 77
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gtaagggtgt cgtgctgatg gccctgtgcg cactgacccg cgctctgcgc tctctgaacc 180
tggcgccccc gaccgtcgcc gcccctgccc cgagtctgtt ccccgccgcc cagatgatga 240
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caccagtgaa gatgaggaag tctgggggcc gagaccacac aggccgaatc cgggtgcatg 420
gtattggcgg gggccacaag caacgttatc gaatgattga ctttctgcgt ttccggcctg 480
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<210> 78
<211> 1113
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1944530CB1

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tagcaaaaca tgttacgttg gttcgagaga gtggctcctt aacttatgaa gaatttctcg 180
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aatcttgggt ggtatcagat gcacccactg aagatgatat ggctaactat attcttaaca 720
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acacaggaaa atccattttc cccactcttt tatttttgct attctgatca tttgtccccc 900
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accatatttt ccattattta tcgttcaaat ttgtatnatt acaactaata gccttgaatt 1020
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1113

<210> 79
<211> 1963
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2019742CB1

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1963

<210> 80
<211> 1089
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2056042CB1

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aaaaaaaaa 1089

<210> 81
<211> 1325
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2398682CB1

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cnagc 1325

<210> 82
<211> 1579
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2518753CB1

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<210> 83
<211> 2641
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2709055CB1

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<211> 3963
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<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2724537CB1

<400> 84

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<212> DNA
<213> Homo sapiens

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<223> Incyte clone 025818CB1

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<211> 2077
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 438283CB1

<400> 86
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<210> 87
<211> 2358

<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte clone 619699CB1

<400> 87
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<211> 1978
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 693452CB1

<400> 88
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<213> Homo sapiens

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<213> Homo sapiens

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<223> Incyte clone 2495790CB1

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<211> 608
<212> DNA
<213> Homo sapiens

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aaaaaaaa 608

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<211> 3257
<212> DNA
<213> Homo sapiens

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<223> Incyte clone 2674047CB1

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<211> 1945
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2762174CB1

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<210> 105
<211> 1829
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2765991CB1

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<211> 1353
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2775157CB1

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<211> 1025
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2918375CB1

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<210> 108
<211> 3641
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 3149729CB1

<400> 108
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<213> Homo sapiens

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<223> Incyte clone 3705895CB1

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<213> Homo sapiens

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<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<223> Incyte clone 319415CB1

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<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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tcgctgtgtt gctcaggctg gtctcaaact cctgagatca agcaatccgc ccacctcagc 2040
ctcccaaagt gctgagatca caggcgtgag ccaccaccag gcctgattgt aatttttttt 2100
tttttttttt tactggttat gggaagggag aaataaaatc ata 2143

<210> 116
<211> 1010
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1427838CB1

<400> 116
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tgagtgactc tttaacgctt gccgtgggaa caggaagatt ttcgggacca ttgcacagag 180
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tagccagtgc agcagcattt tactatgttt ttgaaatcag tgagacttac aacaggctgg 300
ccttggaaca cattcaacag caccctgagg agccccttga aggaaccaca tggacacact 360
ccttgaaagc tcaattactc tccttgcctt tttgggtgtg gacagttatt tttctggtac 420
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<210> 117
<211> 2059
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1448258CB1

<400> 117
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acaagagaag ctgcagcaat gggacctact aagtttacac aaactaatat agggataata 180
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tgacagaagg acctttacat ggcagctaac agtgcttttt gctgaccagg attggtttat 1620
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gaaacattaa aaaaaaaaa 2059

<210> 118
<211> 2273
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1645941CB1

<400> 118
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gctactgagc agaatttcga acagcaggat ttcgtatttt ttgcttccaa ctgcacactt 360
ccgttgccca cttttaaatc agagatacct acactcaaaa cccagacaag gcaaaaggat 420
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cattcatgga aggtagtgcc agtgaagtac tcaaagaatg gacagtaaca ggcaagaaaa 720
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aacttacagt tagatgtaat aacaaaaaga agtttatgcg tatcactttt tgtgccattc 2220
taagtatttt tggtttcttg tctccttatt tcctctttac catttttgga ggg       2273
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<210> 119
<211> 1772
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1646005CB1

<400> 119

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ctatccggga ttcagaatca gctatggaaa cttgagagac ctagagaaaa taacttcttt  180
cactttgaac tgattctttg cttcataaga aaagtattat ccagccacaa aaatggtcaa  240
aattcagatc tacaaaagcc tgtcaggcag aaactgaccc cacttaggcc acgccaatga  300
gcaagtcatc aaagcagcca agacaggtcc tgtgggggcc acccatgcac agggcccagc  360
ctcgggtcct aaccccgcct atgctttccg ccaccataaa gaggcccatc tgggtaagac  420
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gagcagctgg cagctcaagg acatccggag ttggaggatg gagcaatgca ggcccttgtg  540
gtaaagacag tcctgcagcc gcgcaggcag ggatgctgca agtggagtgc caggcgggtg  600
cggagccctg tgggactgtg gaggggtcag agggaagcca ggattttggg gtctctgaga  660
gtttggagaa ggggaagaag attaaagctt gtttcaaaag tttctaatca ggtgggcagg  720
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<210> 120
<211> 2260
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1686561CB1

<400> 120
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<210> 121
<211> 1602
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1821233CB1

<400> 121
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gattgtgtgg tcttttgggg ttttttgttt tttttttttt aagacaaagt tgaccgctgt 1560
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<210> 122
<211> 1655
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1877278CB1

<400> 122

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tgtctgccga gttctcacgt gcccatcagt gacagcaagt ccattcagaa gtcggagctc  180
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cgtgaggaag aagggactct gatcatcgag gggctcctca acattgcctg ggggctgacg  300
cggcccatcc ggctgcagat gcaggatgac cgggagcagg tgcacctccc ctccacctca  360
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gggcccctgg aggaggcaga ggaggccccc cagctgatgc ggaccaagag cgacgccagt  540
tgcatgagcc agaggaggcc caagtgccgc gcccccggtg aggcccagcg catccggcga  600
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<210> 123
<211> 2225
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 1880692CB1

<400> 123
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taanctacnc gatncangnc ggttcangaa acncccnaaa aattggatcn nnttgatcac 120
atgccaagct gatggagtgg ctaaagagta cagattatgg aaaatatgaa ggactaacaa 180
agaattacat ggattattta tcccgactat atgaaagaga aatcaaagat ttctttgaag 240
ttgcaaagat caagatgact ggcacaacta aagaaagcaa gaagtttggt cttcatggaa 300
gttcggggaa attaactgga tctacttcta gtctaaataa gctcagtgtt cagagttcag 360
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aacataattg tggcacacca ctgcctgttt catctgagaa agatatgatc cgccaaatga 660
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cagcagcgtc agccctatcc ggacccgcat cctcctctcg ggccggtgc caacccctag 2160
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cttcc 2225

<210> 124
<211> 1516
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2280456CB1

<400> 124
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gcctgcgcaa gttacgcgaa agctaacaga atctgcggtg ctctgctggc gactggcatg 120
acgcggtgca gagagcggac ttccgcgacg cgggtgtttt tttttacttg aatgtaaata 180
ccaatcaaga tacattgaaa taagaaggtc ctacagtgta ggggaagcaa tggaagaact 240
tctacctgat ggacaaatat gggctaatat ggatccagaa gaacgaatgt tggcagctgc 300
tacagctttt acccacatct gtgcagggca gggtgaagga gatgtcagga gagaagccca 360
atctatccaa tatgatccct acagtaaagc ttcagtagcc ccagggaagc gacctgctct 420
tcctgtgcaa ctacagtacc cacatgtaga aagtaatgtc ccttcagaaa cagtctctga 480
ggcctcccaa agactccgaa agccagtgat gaagagaaag gtgctgcgca gaaagccaga 540
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tgatcaggat ctctgggact taagacaaag gctgatgaat gtacagttcc aggaagacaa 660
ggaatcttca tttgatgttt cacaaaaatt taacctacca catgaatacc aaggaatttc 720
tcaagatcag ctcatttgct ctctacaaag agaaggaatg ggctctccag cttacgaaca 780

agacctgatt gttgccagca gacccaagtc ctttattctc ccaaagctgg accagttaag 840
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ctcaatacgt ttacctggtg aagatcatag aaaggaatta cgctggggtg tccgagagca 960
gatgctttgt cgagcagaac cccaatccaa acctcagcat atatatgtcc caaacaatta 1020
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agcaattgca agataaatca tatcagagaa agaacaacag acctggtctt tctattttgt 1380
caaattagta cgggcccttt gagtcctgta actttttttta cctatcaata tgagttgctg 1440
tgcttcagtg tgtgtttttt aagttgctgg gcattacact taccaattaa agaattttgg 1500
aaattcaaaa aaaaaa 1516

<210> 125
<211> 1635
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2284580CB1

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ggcatggcga ctttttctgg cccggctggg ccaatcctgt cgcttaatcc gcaggaagat 120
gtcgagtttc aaaaggaggt ggcgcaggtt cgcaagcgca taacccagcg aaaaaaacaa 180
gaacaactta ctcctggagt agtctatgtg cgccacctac ctaacctact tgacgaaacc 240
cagatctttt catatttctc ccagtttggc actgtgacac ggttcaggct gtccagaagt 300
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aaaatagttg ctgaaacaat gaacaactac ctgtttggtg aaagactctt ggagtgtcat 420
tttatgccac ctgaaaaagt acataaagaa ctctttaaag actggaatat tccatttaag 480
cagccatcat atccatcagt gaaacggtat aatcggaatc ggacactaac acaaaagcta 540
cggatggagg agcgatttaa aaagaaagaa agattactca ggaagaaatt agctaaaaaa 600
ggaattgact atgattttcc ttctttgatt ttacagaaaa cggaaagtat ttcaaaaact 660
aatcgtcaga cgtctacaaa aggccaggtt ttacgtaaga agaagaaaaa agtttcaggt 720
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acatttttgg agaggcgaaa atctcaagtg gctgaactga atgatgatga taaagatgat 840
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gttaaattag ttttggttgt gctagcatga attaataacc accattttat accagtatca 1560
tcagtgaaga attgtatttc aagattcaaa caataaccag caattaaact tttttctaca 1620
atgtaaaaaa aaaaa 1635

<210> 126
<211> 2673
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 2779172CB1

<400> 126
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gatggtcctt tgccacagct tcctttaccg tatattaaca gttcagcaac acgggttttt 120
ttttggccat gacagacgac cagcggatgg tgaaaaacaa gcagctactc atgtaagtct 180
tgatcaagaa tatgattctg aatcctctca gcagtggcga gaacttgagg aacaagttgt 240
ttctgtggtt aacaaaggag taattccatc caattttcat cccacacaat actgtttgaa 300
cagttactca gataattcaa gatttccact tgcagttgta gaagaaccaa ttacagtgga 360
agtggctttt agaaaccctt tgaaagttct acttttgttg actgatttgt cattgctttg 420
gaagtttcat cctaaagatt tcagtggaaa ggataatgaa gaagttaaac aactagttac 480
aagtgaacct gaaatgattg gagctgaagt tatttcagag ttcttaatta atggcgaaga 540
atcaaaagtg gcaagactaa agctctttcc ccatcacata ggggagctgc atattctggg 600
agttgtttat aatcttggca ctattcaggg ctctatgaca gtagatggca ttggtgctct 660
tcccggatgt cacacaggaa aatattcctt gagtatgtca gtccgaggga agcaggattt 720
agaaattcaa ggtcctcgac ttaacaacac aaaagaagag aaaacatctg ttaaatatgg 780
ccctgatcga cgtttagatc ccataatcac agaagaaatg ccactgttgg aggtgttctt 840
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ctcaaggcca tcagtagagc agctttctag tctcattaaa acgagtcttc actacccaga 2040
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gtgcacctta ttaagcccca tcttaagaga aca 2673

<210> 127
<211> 2206
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 3279329CB1

<400> 127
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tgtcatgaag ctccttgtgg gctctgcatg aagctgctgc tttgttttg ggttaacaga 180
tgtgcctgtc aactagcatg tgtattgtcc aaattccata aacttaaggt ttttaagggc 240
tgtgtggttt ctgagctcta tgtgtctttc ctatccttgt accttcaaag ggtgagaaat 300
gagatttata catccaaagt tagtctgata aatatggctt tttgtttctc catgtaacct 360

agactgtcaa aaataagtga tggtgataag taggcctgga gcctcagctt ctgtaaatct 420
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<210> 128
<211> 1426
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 3340290CB1

<400> 128
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ttccnctcnc gnctcccctt ccgcgcncct cccgccggag atgaggggaa gatgtccgtg 120
tcagggctca aggccgagct gaagttcctg gcgtccatct tcgacaagaa ccacgagcga 180
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gaagaagagg aagaagaaga agagatggct gaagatatag aagacttaga tcactatgag 480
atgaaggaag aagagcctat tagtgggaaa aagtcagagg atgaaggaat tgaaaaagaa 540
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taaagcagcc aagtcaacat caggctactg aagttgaggc tttangggta ctttcctata 1380
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<210> 129
<211> 1703
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte clone 3376404CB1

<400> 129
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tggtggcacc tgcctgtaat cccagctact caggaggctg aggcaggaga atggcttgaa 180
cctgggagac ggagcttgca gtgagccgag attgcgctcc agcctgggcg acagagcgag 240
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(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications

US	60/084,254 (CIP)
Filed on	5 May 1998 (05.05.98)
US	60/095,827 (CIP)
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(54) Title: HUMAN TRANSCRIPTIONAL REGULATOR MOLECULES

(57) Abstract

The invention provides human transcriptional regulator molecules (HTRM) and polynucleotides which identify and encode HTRM. The invention also provides expression vectors, host cells, antibodies, agonists and antagonists. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of HTRM.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/09935

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 C07K16/18 C12Q1/68 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HILLIER ET AL.: "WashU-NCI human EST Project" EMBL ACCESION NO AA190560, 21 January 1997 (1997-01-21), XP002114035 the whole document ---	3-13
A	US 5 739 010 A (SHAH PURVI ET AL) 14 April 1998 (1998-04-14) column 30, line 24 -column 32, line 45 column 1, line 28 -column 2, line 23 ---	1-20
A	FREIMAN ET AL: "Viral mimicry: common mode of association with HCF by VP16 and the cellular protein LZIP" GENES AND DEVELOPMENT, vol. 11, December 1997 (1997-12), pages 3122-3127, XP002114036 figures 1,4 -----	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 1999	17.12.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	van Klompenburg, W

Form PCT/ISA/210 (second sheet) (July 1992)

Int .tional application No.
PCT/US 99/09935

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 19 and 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

See FURTHER INFORMATION Sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

See additional sheet, Invention 1.

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The subject-matter of claims 17 and 18 and of claim 20 in so far as it relates to antagonists is insufficiently characterized. A meaningful and complete search could therefore not be performed for said claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-20 partially

A substantially purified polypeptide according to SEQ ID NO 1 or a polypeptide with at least 90% identity or a fragment thereof. Methods for producing said polypeptide. Antibodies, antagonists and agonists of the said polypeptide. Methods of treatment using said polypeptides or antagonists.
An isolated polynucleotide encoding said polypeptide or an isolated polynucleotide with 70% identity to such a polynucleotide or a polynucleotide according to SEQ ID NO 66 and fragments of said polynucleotides.
Methods for detecting said polynucleotides.
Expression vectors comprising said polynucleotides and host cells comprising said expression vectors.

Inventions 2 to 65, claims: 1-20 partially

idem for SEQ ID NO 2-65 and the corresponding nucleotide sequences from SEQ ID NO 67-130.

INTERNATIONAL SEARCH REPORT

Inf ation on patent family members

Internatio Application No
PCT/US 99/09935

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5739010	A	14-04-1998	NONE	

Form PCT/ISA/210 (patent family annex) (July 1992)